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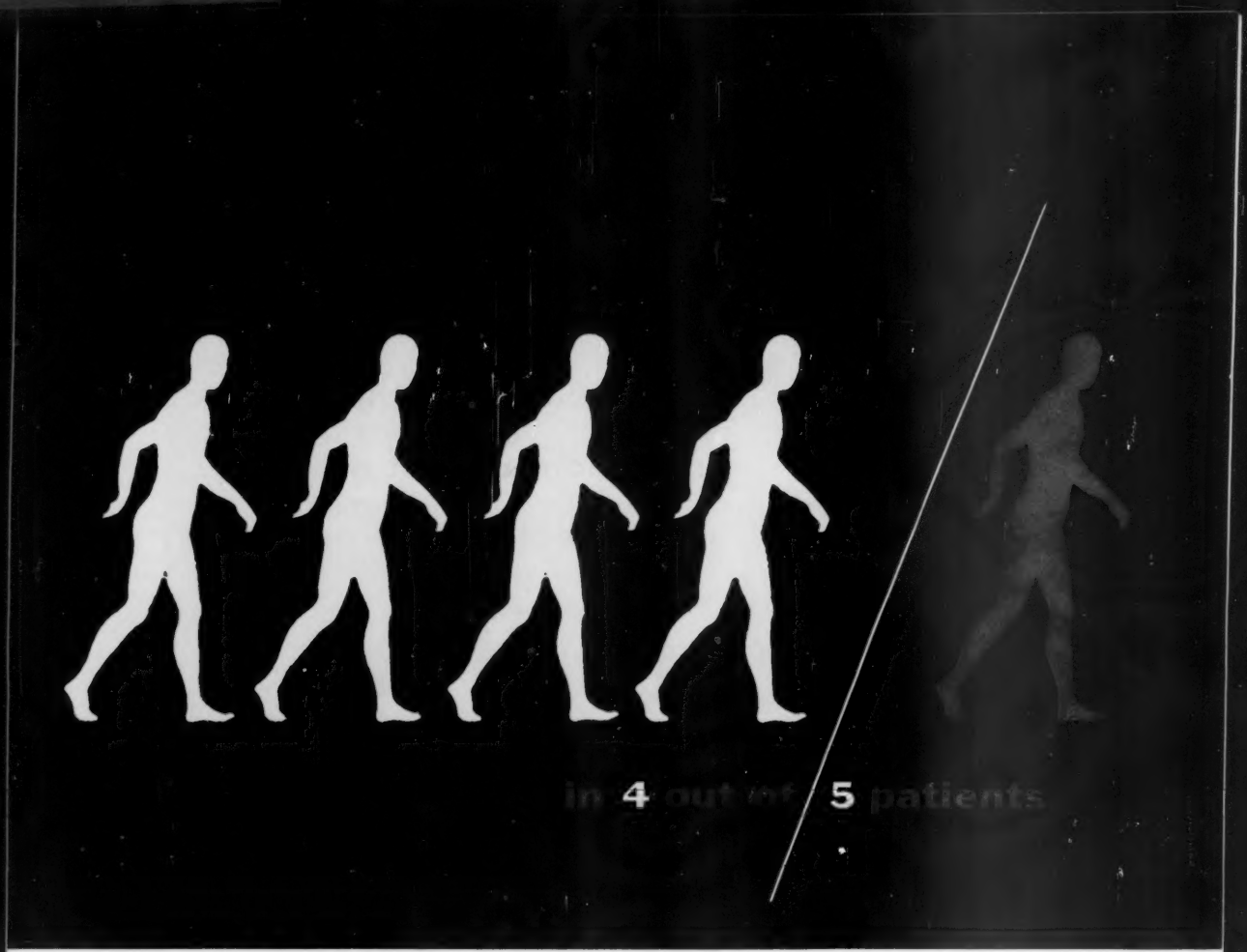

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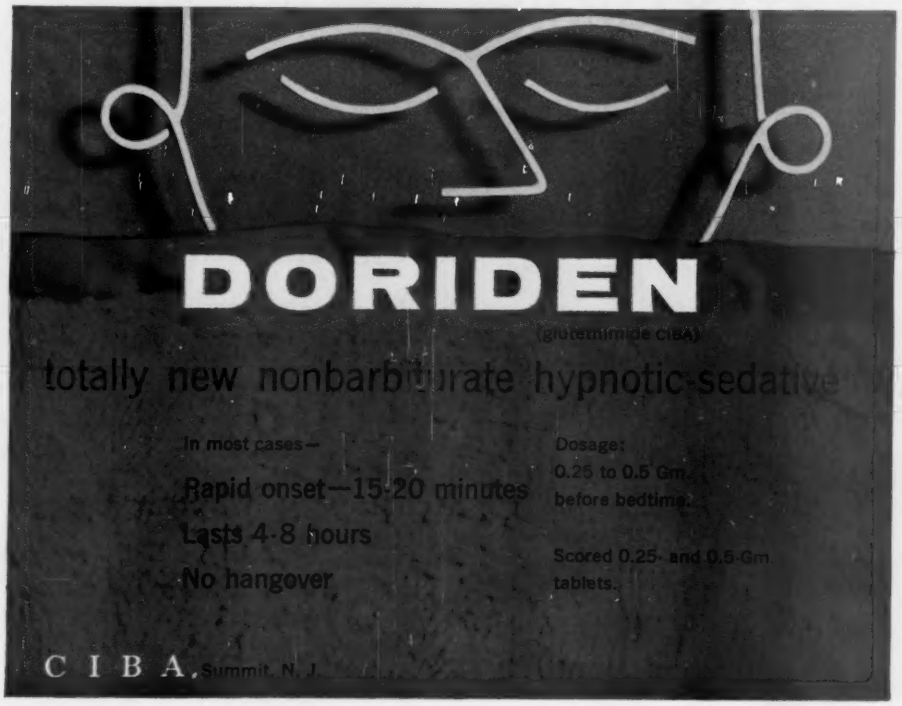

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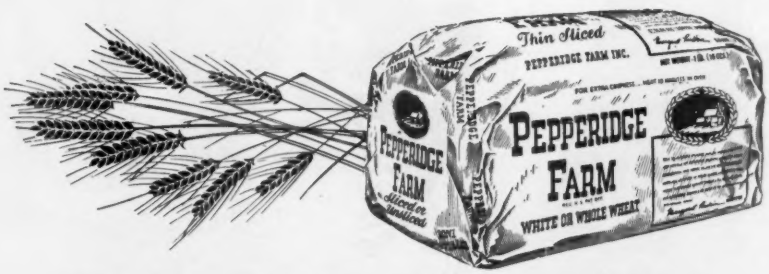

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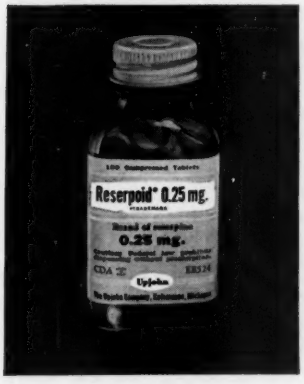

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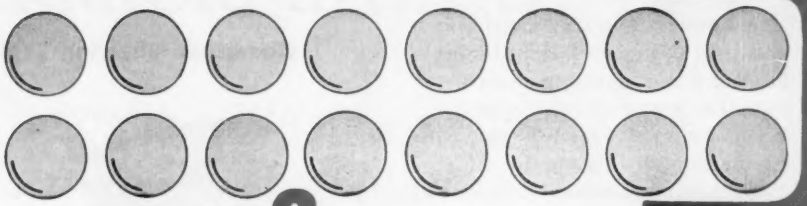

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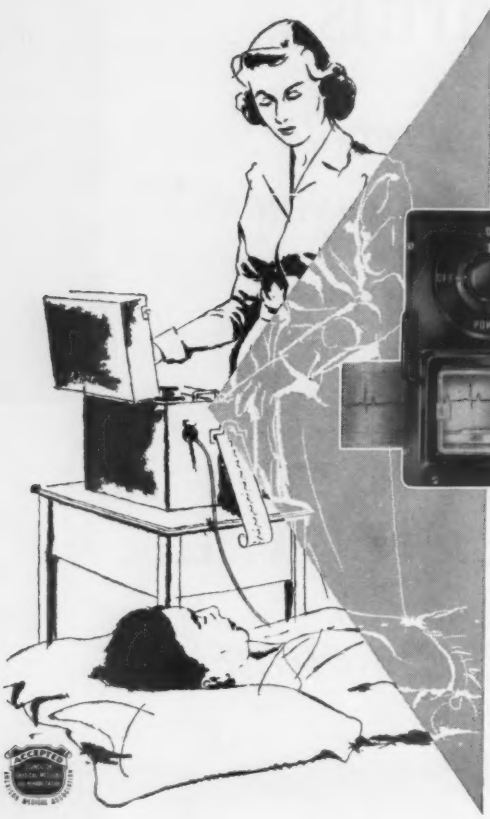

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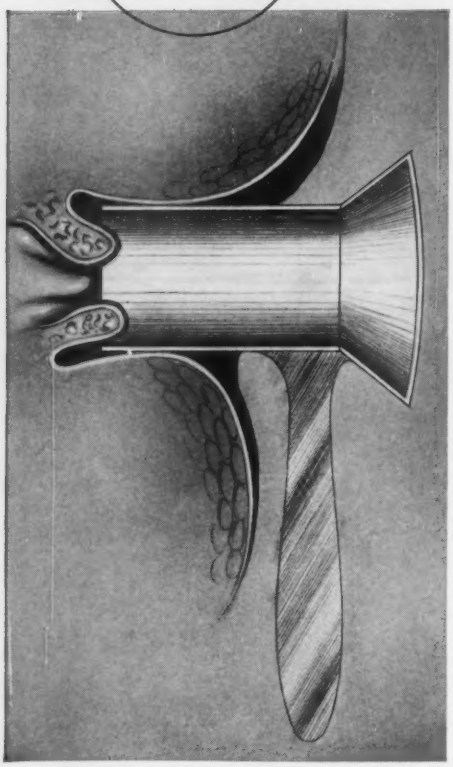

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Volume 253 JULY 28, 1955 Number 4

CUSHING'S DISEASE*

The Surgical Experience in the Care of 46 Cases

OLIVER COPE, M.D.,† AND JOHN W. RAKER, M.D.‡

BOSTON

IN his classic monograph on the pituitary gland published in 1912 Harvey Cushing[1] described the case of a young woman with a disorder that has come to bear his name. The patient suffered from headaches and backache. She was obese about the head, neck and trunk, but her extremities were thin. Her back was bent over, her complexion was florid, and she suffered from hirsutism, amenorrhea and diabetes. He suggested that the disease was in some way related to the pituitary gland but also recognized that the adrenal glands might be involved because he found at least 1 similar case in the literature in which an adrenal tumor had been found at autopsy.[2]

Not until 1930 did Cushing see another patient with a comparable disturbance, this time a man thirty years of age. He was able to cull from the literature, between 1913 and 1930, 9 cases in which no significant tumor of the adrenal gland had been found at autopsy. In 4 a basophilic adenoma of the anterior pituitary body had been discovered. In a fifth a cluster of basophilic cells representing a probable adenoma was present, and in only 1 case in which an adequate search had been made was no adenoma found. In spite of reports of other cases with a comparable clinical disturbance associated with an adrenocortical tumor but no evidence of pituitary abnormality, Cushing concluded that the disturbance was a pluriglandular one with the anterior pituitary adenoma playing the dominant or etiologic role.

On the basis of this concept the pituitary gland of Dr. Cushing's second patient was irradiated. During two months of observation his condition had been deteriorating. Immediately after the therapeutic irradiation the patient felt better and during the next year reported slow, continued improvement.

Further exciting confirmation of Dr. Cushing's concept came in the next year, 1931, when Teel predicted and found a minute basophilic adenoma in the anterior pituitary body of a young woman with this syndrome who had died of meningitis. Teel had been a tutorial student with Dr. Cushing during 1929 and was aware of Dr. Cushing's thinking.

In 1932 Cushing described his concept of the disease in an article[3] in which he recorded his 2 cases and summarized the evidence from the 10 cases reported in the literature. Six months later he reported 4 more cases, including another studied by himself.[4] This last patient was also treated by irradiation of the pituitary body, after which she was promptly and completely relieved of the disease. The case for pituitary basophilism seemed well established.

The experience with Cushing's disease at the Massachusetts General Hospital since 1935 has led us to question the concept held by Cushing. Pituitary irradiation has proved inadequate therapy. The attempt by Albright to inhibit the anterior pituitary body with testosterone seemed promising at first, but it too has failed. Surgical resection of the adrenal glands has come to be the most reliable treatment, and with increasing experience and the advent of cortisone it promises to be a therapy equal to the surgical therapy of hyperthyroidism. A résumé of the trends of our thinking and of our experience follows.

The first patient with Cushing's disease recognized at the Massachusetts General Hospital entered the hospital in August, 1935. She was promptly treated by pituitary irradiation but failed to improve. She died five months later, and a malignant tumor of the adrenal cortex with metastases was found. The anterior pituitary body did not contain an adenoma. Our confidence in Dr. Cushing's concept was shaken by this experience. Our doubts were further supported by reports of at least 2 similar cases.[5,6]

In spite of our shaken confidence the next 2 cases were also treated initially by pituitary irradiation. Careful x-ray studies of the adrenal glands had been made before the irradiation in an effort to exclude the presence of an adrenal tumor. These 2 patients,

*From the Department of Surgery, Harvard Medical School, and the Surgical Services, Massachusetts General Hospital.

The work described in this paper was supported in part by a grant from the American Cancer Society and in part by Departments of the Army and Navy, NR 114-198.

†Associate professor of surgery, Harvard Medical School; visiting surgeon, Massachusetts General Hospital.

‡Director of surgery, Pennsylvania Hospital, Philadelphia; formerly, associate in surgery, Harvard Medical School, and assistant in surgery, Massachusetts General Hospital.

Cases 2 and 3,* also failed to benefit by irradiation. Their adrenal glands were therefore explored surgically in 1936 and 1938 respectively. The presence of a tumor was excluded in each case, and in an effort to reduce the cortical function approximately a third of each adrenal gland was removed. A more radical resection was deemed unwise because of the fear of adrenocortical insufficiency. Neither patient was improved.

Our fourth patient (1938) had an obvious tumor of the adrenal cortex on a roentgenogram. This patient died with a pulmonary embolus and adrenocortical insufficiency after subtotal resection of the tumor.

The next 2 patients (1940 and 1942) were studied by periadrenal air injection, and no evidence of tumor found. They were treated, therefore, by pituitary irradiation, again without benefit.

The failure of both pituitary irradiation and partial adrenalectomy to benefit patients without evidence of adrenal tumor suggested to Albright and his associates[7] the advisability of trying hormone therapy to inhibit the anterior pituitary body. It was thought that testosterone, estrogen or desoxycorticosterone acetate might inhibit the excessive corticotrophic activity of the anterior pituitary body much as estrogens and testosterone relieved the excessive follicle-stimulating action of the gland in postmenopausal women. Testosterone was selected as the first hormone to be tried because of its known effect on nitrogen balance. It was assumed that patients with Cushing's disease should be in negative nitrogen balance, and it had been demonstrated that testosterone induces a positive nitrogen balance and muscular growth in eunuchoid patients.[7,8] In this manner testosterone might aid in the recovery of the muscular weakness of Cushing's disease.

One of the first 2 patients injected with testosterone went into positive nitrogen balance, and there was an apparent clinical remission. It is possible that there was a later exacerbation of the disease, for the young woman died in cardiac failure four months after omission of the testosterone. Subsequent patients treated with testosterone have not been relieved, and at least 2 patients have become edematous while on therapy, one dangerously so. Testosterone has not proved effective, therefore, as the definitive therapy.

Estrogens, DOCA and cortisone have also been tried; they too have failed to suppress pituitary activity and have not led to replenishment of tissues. DOCA in particular led to complications interfering with subsequent therapy.†

Although cortisone did not suppress the hormonal overactivity of Cushing's disease, cortisone and ACTH have provided the final confirmation of the concept that the adrenal cortex produces the clinical and biochemical characteristics of the syndrome. All the known manifestations of Cushing's syndrome have been reproduced in patients with arthritis and other medical conditions after continued therapy with either ACTH or cortisone.[9] Cortisone has also contributed by adding to the security of the operative management of Cushing's disease.

Reliance has ultimately had to be placed on surgical resection of adrenocortical tissue. With increasing experience the results of surgical therapy have improved to a new level of confidence. An understanding of the pathology of the disease in the adrenal gland has evolved. When a tumor is present it alone is removed. When bilateral hyperplasia is the pathologic type, subtotal resection of both adrenal glands has become the operation of choice in our hands. The surgical approaches to the adrenal gland have been explored, and the advantages of each determined.

This introduction has been a recounting of personal experience. In it we have referred only to articles in the literature that appeared at the time to influence the development of our thinking. There are a number of other articles to which we should have referred if this review were to be inclusive. It would be remiss not to mention, however, the profitable informal exchange of thoughts that we have had over the years with many and in particular with Drs. Kepler and Keating, of the Mayo Clinic. The experience of the Mayo Clinic has recently been recorded by Sprague, Kvale and Priestley,[10] and by Walters.[11] It and our own have run closely parallel.

Symptoms and Physical Changes

The diagnosis of Cushing's disease is readily made when the disease is full blown. So characteristic are the physical changes brought about by the pathologic process that the diagnosis can be established on clinical examination alone without resort to laboratory confirmation. Difficulty in diagnosis comes, however, when some of the features of the disease are missing or not fully developed. Many of our patients had consulted physicians for a variety of complaints over a period of years before the diagnosis of Cushing's disease was even considered. Not until the disease had progressed further or until other diagnoses had proved inadequate was Cushing's disease considered.

The patients with fully developed Cushing's disease have been striking caricatures of their former selves. Comparison of their photographs before the onset of the disease with the appearance in the diseased state led the untrained eye to doubt the identity of the patient.

The diagnosis of Cushing's disease in its milder forms has depended on an awareness of the variability of the clinical picture. The onset has usually been insidious, and the early symptoms were nonspecific. Even the outstanding features of the disease have been inconstant. Symptoms and physical changes depend on the intensity of hormonal imbalance and the rela-

*The case numbers of the patients with Cushing's disease from this hospital are arranged in the order in which they were encountered. The same case numbers will be used in future publications from this hospital.

†ACTH was not included in the hormones tried because of the possibility that it might stimulate the growth of any tumor present and the probability that it might make the disease worse and endanger the life of the patient.

tive prominence of the effects of the various individual adrenocortical hormones. The roentgenographic and laboratory abnormalities likewise depend on the degree and character of the hormonal imbalance.

A multitude of symptoms were encountered in our 46 patients. The presenting complaint of each patient and the frequency with which these and three other common symptoms were encountered in all the patients are recorded in Table 1. In addition a variety of symptoms were acknowledged, each symptom in only one or a few patients. Each system of the body was involved. Six patients had either dyspnea or palpitation. Two complained of deafness, one of dizziness and 2 of sweating. One suffered from a dermatitis, and one from falling hair, and 3 had sufficient acne to have been seriously troubled by it. Eight patients had had renal colic, but only one polydipsia and one nocturia. One patient had had a hemorrhage from a duodenal ulcer. Only 3 had lost sufficient weight to complain of it. A girl had had a precocious puberty, and a woman premature hot flashes. One woman had noticed the abdominal mass of her adrenal cancer, and a man the severe flank pain of his. Three had worried about their loss of weight, but only one had been aware of a fracture of a bone.

The predominant physical changes of the disease are a pecular obesity, a florid atrophy of the skin, hirsutism, acne, muscular wasting, vascular fragility, hypertension, osteoporosis and gonadal suppression. The obesity is characteristically limited to the head, neck and trunk. The face becomes puffed out and rounded to the so-called "moon-face" (Fig. 1*A* and 1*B*). The supraclavicular fat pads and the buffalo hump are prominent. The entire trunk is obese. Curiously enough, the extremities are wasted and do not share in the excessive fat.

Not all our patients had this obesity. One of the women past fifty (Case 26) and the youngest man (Case 35) showed little or none. Change in weight is an unreliable guide to its presence because its development may be compensated for by loss of weight in muscle, bone and perhaps other tissue.

The entire skin of the body is atrophied. The thinning appears to be predominantly of the corium. The vessels of the skin are prominent; the face appears florid, and the skin of the extremities has a blotchy appearance called "marble skin." The strength of the corium is reduced so that it yields under the normal forces exerted upon it and pulls apart, and striae are produced. Striae may thus be considered to be pathologic fractures of the corium. The subcutaneous veins show through the intact epidermis, giving a purplish color. These striae are found on the abdomen, hips, flanks and breasts and across the lower axillae. They were absent in nearly a third of our patients. Breaks in the skin over the shins, with slow healing, and pigmentation have been encountered in several, including 2 of the younger patients. Acne of the face and of the trunk has been common.

When present, hirsutism has been a helpful sign in women. It has usually been accompanied by recession of the temporal hair. In men the growth and distribution of hair has not been helpful diagnostically, but in one of our male patients (Case 35) an increase in rate of beard growth required shaving twice a day.

Muscular wasting has been the most constant sign in our patients. It leads to fatigue, the most consistent symptom. We would hesitate to make a diagnosis of Cushing's disease if it were absent. It is the most reliable diagnostic distinction between this disease and other obesities with striae, hypertension and gonadal suppression.

TABLE 1. *Complaints of the 46 Patients.*

SYMPTOM	PRESENTING COMPLAINT	AS ADDITIONAL SYMPTOM	TOTAL OCCURRENCE
	NO. OF CASES	NO. OF CASES	NO. OF CASES
Fatigue & weakness	16	19	35
Weight gain & obesity	6	28	34
Changed appearance	2	31	33
Amenorrhea or irregularity	3	26	29
Bruising		18	18
Nervousness, depression, irritability	4	11	15
Back pain & bone pain	5	9	14
Hirsutism	3	10	13
Headache	1	9	10
Ankle & hand edema	1	8	9
Libido (females); impotence (males).		8	8
Paresthesias	1	3	4
Lower voice		4	4
Blurred vision	1	2	3
Poor wound healing & leg ulcers	1	2	3
Cessation of growth	1		1
Difficulty in walking	1		1
General aching & malaise	1		1

Vascular fragility and hypertension are common. Most of our patients had observed the frequent appearance of cutaneous and subcutaneous bruises after minimal or unnoticed trauma. Two of our patients developed massive deep hematomas before correction of the hyperfunction of the adrenal cortex. Significant hypertension was present in approximately half of our patients and mild or moderate in another quarter. Several had been diagnosed and treated for essential hypertension before the Cushing's disease had been recognized. Screening of all patients with hypertension for Cushing's disease is indicated.

Related to the hypertension, and also in all probability in part to the electrolyte and metabolic disturbances, is a stubborn edema of the ankles.

Osteoporosis is a cardinal sign, but it has not always been present. Skeletal pain, and in particular, backache have been accompaniments. When the osteo-

porosis was severe, collapse of vertebral bodies had often occurred, and nerve-root pain was distressing. The negative calcium balance accompanying the osteoporosis led to the formation of renal stones in 11 of our patients (silent in 3).

Gonadal suppression has led to complaints, and its effects on both primary and secondary sex organs have been obvious on physical examination. It was not always present; 3 of our patients conceived and bore normal children during active phases of the disease. In the males loss or decrease of libido was common.

The other endocrine changes rarely led to symptoms or recognizable physical abnormalities. The rare diabetes mellitus, present in only 5 cases, was severe enough in only one to lead to polydipsia and polyuria (Case 2). The thyroid suppression has been so mild that any symptoms and signs that might have been induced were overshadowed by others.

TABLE 2. *Distribution According to Age and Sex (46 Cases).*

AGE	MALE PATIENTS	FEMALE PATIENTS	TOTALS
yr.			
0- 9	1	0	1
10-19	0	4	4
20-29	3	7	10
30-39	4	12	16
40-49	0	9	9
50-59	0	2	2
60-69	2	1	3
70-79	0	1	1
Totals	10	36	46

In 13 of our 46 patients mental difficulties were prominent among the symptoms. The patients themselves had noted that they were unreasonably irritable and that they could not concentrate. Those who were in school found their performances in learning impaired. In several these changes have been so striking that they constituted the major problem in the management of the patient. Several had been labeled psychoneurotic. In 2, a diagnosis of schizophrenia had been made. One of these was confined to a mental institution and had been receiving electric-shock treatment at the time when the disease was recognized by Dr. Hannibal Hamlin, a member of our neurosurgical staff.

The patients appear to be more susceptible to infection than are normal persons. Infections have been a major complication of management. Moderate acne of the skin is common in these patients; 1 had serious undermining sepsis of the skin that required intensive antibiotic therapy and surgical drainage. Another developed a tubo-ovarian abscess with extending peritonitis requiring surgical drainage. Yet another developed acute cholecystitis while being prepared for adrenal surgery.

The disease is rare, but we have the impression that it is more common than it was originally thought to be. As the diversity of the clinical picture is understood it is to be expected that more cases will be found. Of the 46 patients treated at this hospital in the past 19 years, 10 were seen in the first ten years, and 36 in the subsequent nine years. The greatest number in any year, 7, were seen in both 1952 and 1953. This upward curve of hospital incidence probably represents the rising tide of recognition rather than an increasing incidence of the disease.

The condition is much more common in females than in males, for among these 46 patients only 10 were men. The age varied from nine months to seventy-six years, but the disease is one predominantly of young adults, for the average age of the whole group was thirty-four and eight-tenths years. Table 2 shows the sex and age distribution by decades.

FIGURE 1. *Moon Face of a Thirty-Year-Old Woman with Cushing's Disease of Mild Degree — the Floridity is Absent, and the Hirsutism Slight (Case 29).*
A = *preoperative appearance.*
B = *Appearance four years after the removal of a benign cortical adenoma.*

FIGURE 2. *Grossly Normal Left Adrenal Gland Removed Surgically from a Forty-Six-Year-Old Man with Hypertension of a Kind Not Improved by Total Adrenalectomy.*

FIGURE 3. *Grossly Normal Left Adrenal Gland Removed Surgically from a Forty-Nine-Year-Old Woman with Metastatic Carcinoma of the Breast.*
The convolutions may have been exaggerated beyond the normal for a patient of this age by castration two years previously.

FIGURE 4. *Diffusely Hyperplastic Adrenal Glands Subtotally Resected from a Twenty-Four-Year-Old Man (Case 35).*
The glands are enlarged, the cortex thicker, and the convolutions more exaggerated than in the normal person. There are globules of extracapsular cortical tissue on both sides.
A = *external appearance of the right.*
B = *cut section of the left. Both the outer yellow and inner brown zones of the cortex are thickened. The glistening gray medulla stands out in the tips of the left-hand section.*

FIGURE 5. *Nodular Hyperplastic Right Adrenal Gland of a Forty-One-Year-Old Woman with Severe Cushing's Disease of Four Years' Duration (Case 39).*
The gland contained several encapsulated nodules, which are visible externally (A) and on cut section (B). The cortex between the nodules is hyperplastic rather than atrophic. An extracapsular nodule is also visible.

FIGURE 6. *Benign Adenoma of a Sixteen-Year-Old Girl (Case 43).*
A = *external appearance.*
B = *cut section.*

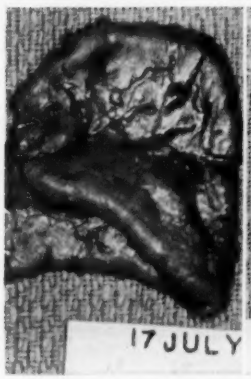
FIGURE 7. *Malignant Tumor of a Sixty-Year-Old Man (Case 37).*
The primary tumor is dark brown and occupies the upper portion of the picture. In the perirenal fat excised with the tumor lie several similarly colored, enlarged, invaded lymph nodes.

1A

1B

2

3



4A

4B

5A

5B

6A

6B

7

Several patients dated the onset of their symptoms from the time of an emotional crisis. The symptoms of a number of others started near the termination of a pregnancy, and in still others near the menopause. The disease is primarily one of women of the childbearing period. The possible etiologic role of emotional and endocrine factors is discussed in the final section of this report under Comment.

Anatomic Pathology

Pathologic changes in Cushing's disease are evident in the supporting tissue of mesenchymal origin and in the endocrine glands. Abnormalities of epithelial tissues other than those of the endocrine glands have not been described. Whether the alterations in the brain are limited to the supporting tissues or involve various nerve cells remains to be elucidated.

Supporting Tissues

The keynote of the change in the supportive tissues is atrophy; we have found it throughout the body. In the skin it takes the form of thinning of the corium and the development of striae. The subcutaneous tissues become so lacking in fibrous supporting tissue that fascial layers normally thick and tough become almost like tissue paper in consistence and strength. This is striking during the course of any surgical procedure on these patients. The surgeon observes that his hemostatic clamps actually tear through tissues and fall away from the wound under their own weight.

In contrast to this atrophy the subcutaneous tissues are distended with fat. The peculiar distribution of this fat has already been mentioned. The muscles become flabby, thin and often grossly infiltrated with fat.

The blood vessels both large and small are similarly lacking in resilience and strength. These changes presumably account for the easy bruising and tendency to hemorrhage that we have seen in these patients. Advanced arteriosclerosis of peripheral vessels is not uncommon. The atrophy of bone matrix is striking. The bones become extensively decalcified, and pathologic fractures were the rule in the patients in whom the disease had progressed beyond the early stages. At operation the ribs fragmented as they were being resected.

Brain and Viscera

Two of the patients gave evidence of atrophy of the brain. In one, autopsy revealed a small brain and general dilatation of the ventricular system, and in the other a pneumoencephalogram demonstrated ventricular dilatation and cerebral atrophy; this patient is still living. The findings in these 2 patients have been described elsewhere, and other cases of such atrophy are recorded in the literature.[12] The relation between this atrophy and Cushing's disease is not clear. It may represent in the brain the process comparable to that in the supporting tissues. There is no evidence that it causes Cushing's disease. It is possible that changes will be found eventually in the hypothalamus or elsewhere in the brain, indicating a locus of stimulation that ultimately affects the adrenal cortex. Such changes have already been claimed by Heinbecker[13] and postulated on experimental grounds by Hume,[14] but denied by others.[15]

We have not observed a pattern of alterations in the gastrointestinal tract, and none has been described in the literature. In one of our male patients a duodenal ulcer had been found on roentgenographic examination.

Endocrine Glands

An adequate description of the pathologic anatomy of the endocrine system of the patient with Cushing's syndrome has still to be written. At the present moment certain gross changes in the endocrine glands are recognizable. They are found in the adrenal glands, the thymus and the ovaries. However, the changes in the adrenal glands visible to the surgeon's eye have not been fully corroborated on microscopical section by the pathologist, and it has been impossible to obtain general agreement about the significance of alterations in the other endocrine glands, including the anterior pituitary body.

The anterior pituitary body. The state of the anterior pituitary body in Cushing's disease is still *sub judice*. No consistent enlargement comparable to that found in acromegaly has been recorded. None of our patients showed enlargement of the sella turcica by roentgenogram; there was no enlargement of the anterior pituitary body in the 7 examined at autopsy.

The 7 pituitary glands examined gave no evidence of a basophil adenoma. One contained a small nonbasophilic adenoma.[16] Differential cell counts have been made by Dr. Russfield on the other 6. These 6 contained the Crooke's hyaline basophils and abundant hypertrophic amphophils described by Mellgren[17] as characteristic of adrenal hyperactivity. There was no increase in well granulated basophils in any of the 6, and none had hypophyseal adenomas of any description. A separate report of these studies will be made by Russfield.[18] It is our impression, therefore, that the position taken by Rasmussen[19] is correct: that the minute basophilic adenomas believed by Cushing to be responsible for the disease may have been incidental findings.

The adrenal cortex. It is our experience that the adrenal cortex is enlarged in every case either by hyperplasia or by neoplasia. Hyperplasia is the most common anatomic change encountered, and it involves diffusely the cortex of both glands (Table 3). Twenty-seven of our 46 patients proved to have this type of pathology. The hyperplasia may be moderate or exaggerated with large nodules.

The gross enlargement in glands without large nodules is of such moderate degree that on first acquaintance it is difficult to be sure of its presence (Fig. 4*A* and *B*). It is most easily recognized by observing the thickness of the comb of the gland rather than looking at the flat surface. In the average case the thickness is about doubled over the normal. The undulations of the cortex are also exaggerated; here and there minute adenomalike nodules are to be seen. These small nodules are sometimes encountered in the normal gland, but in hyperplasia they are more numerous and thickened. They range from 1 or 2 mm. in diameter to double or treble that size.

TABLE 3. *Pathologic Types of Adrenal Disorder (46 Cases).*

TYPE		NO. OF CASES
Hyperplasia		27
Non-nodular	25	
Nodular	2	
Neoplasia		17
Adenoma	12	
Carcinoma	5	
Unclassified		2
No operation or autopsy	2	
Total		46

In 2 of our most recent cases of hyperplasia (Cases 39 and 41) large nodules were present in both right and left glands (Fig. 5*A* and *B*). The nodules measured up to 2 cm. in diameter. The cortex between the nodules was hypertrophied, not atrophic, indicating the diffuse nature of the process. This type we are calling nodular hyperplasia.

The gross appearance of the cut section of the hyperplastic cortex is particularly characteristic. The cortex of the normal gland* consists of an outer bright-yellow zone 1 mm. thick and a very thin, scarcely visible inner zone of dark brown (Fig. 2 and 3). Inside of this lies the more gelatinous gray medulla. In the hyperplasia not only is the outer yellow zone thickened but also there is an equally broad zone of the inner dark brown, the whole cortex measuring 2 mm. or more (Fig. 4*A* and *B*). It is this inner dark zone that is most characteristic,[20] and we believe that it has been mistaken by some for medulla.†

Separately encapsulated pieces of accessory cortical tissue have been encountered frequently in our patients with Cushing's disease with adrenal cortices of the hyperplastic type (Fig. 5). Such accessory tissue is hard to find in the normal person, and it is conjectured that the tissue is visible in the patient with Cushing's disease because each piece represents an embryologic rest enlarged by the hyperplastic stimulus of the disease. These findings are further evidence of cortical hyperplasia.

Until recently microscopic evidence has been lacking to support a diagnosis of adrenocortical hyperplasia. Although the gross appearance of the adrenal cortices at the operating table has seemed to warrant such a diagnosis, routine methods of study have failed to demonstrate consistent changes in the cellular pattern or in the thickness of the cortex that our pathologists could confidently describe as hyperplasia. Recent utilization of histochemical methods has made it possible to recognize changes consistent with hyperplasia. These are to be described elsewhere by Cohen, Chapman and Castleman.[24] The problem has been made difficult by the fact that the normal adrenal cortex varies in thickness from one gland to another and in different areas of the same gland; the cell pattern also varies. The grossly thickened cortex and the adenomalike nodules particularly well developed in Cases 39 and 41, however, have been so striking that surgeon and pathologists are finally reaching agreement.

Neoplasms of the adrenal cortex causing Cushing's syndrome are both benign and malignant. Benign adenoma has been the second most common lesion in our series (Fig. 6). This type has been found in 12 cases (Table 3). In 1 patient, 3 adenomas were present. At operation an adenoma the size of a hen's egg was found in the left adrenal gland, with a small satellite adenoma of 8 mm. diameter immediately adjacent to it. The intervening cortex was atrophic. At autopsy a third and even smaller adenoma was found in the otherwise atrophic right adrenal gland (Case 9).

A single adenoma was resected in 9 cases. The presence of a second adenoma was excluded in 1 by autopsy and in 4 by surgical exploration of the contralateral adrenal gland. It is theoretically possible that a second adenoma exists in the other 4, but if it does it must be of small size and low secretory power since the disease has been relieved by the excision of the single adenoma.

A malignant neoplasm was the least common pathologic type of adrenocortical lesion found in this series. It was encountered in but 5 patients. The tumor grossly extended in all 5 to neighboring tissues, to the lymph nodes or to liver, lung and bone (Fig. 7). Three had metastases to lung, 2 to liver, and 1 to bone.

Regarding the possible relation between primary hyperplasia of the cortex and subsequent neoplasia, we can only conjecture. There is strong experimental evidence that development of benign and malignant tumors of the thyroid gland follows long-continued stimulus to hyperplasia.[25] Comparable experimental evidence is accumulating regarding tumors of the

*These "normal" glands were removed from patients with widespread metastatic cancer of the breast.

†The gross appearance of the cut section of the hyperplastic adrenal cortex of these patients with Cushing's disease suggests a diminished amount of the medulla. The apparent diminution in amount of medulla may be due either to the relative hypertrophy of the cortex or to atrophy of the medulla. One might speculate that atrophy might well be induced. The reciprocal physiologic relation between the adrenal medulla and adrenal cortex mediated through anterior pituitary action has been described physiologically,[21,22] and discussed in the report of a case of pheochromocytoma from this hospital.[23] In that case the possibility was suggested that an adenoma of the adrenal cortex was due to an excessive adrenocorticotrophic activity of the anterior pituitary body initiated by the increased epinephrine output from the pheochromocytoma. If the converse situation occurs, excessive adrenocortical activity in Cushing's syndrome might induce atrophy of the adrenal medulla.

adrenal cortex. The frequency of benign adenomas of the adrenal cortex is much increased in certain animal species by castration early in life, and in a susceptible strain of mice, malignant tumors are found.[26]

Atrophy of the undiseased contralateral adrenal cortex and of the uninvolved portions of the gland containing the adenoma was invariably present in all our patients with hyperfunctioning cortical tumors. This atrophy is readily recognizable by the surgeon. The architecture of the uninvolved adrenal tissue is fine and delicate. The gland is shrunken in all diameters, and the comb may be thinned to 1 mm. in thickness. The color is the same bright yellow of the normal or hyperplastic gland. On cut section the cortex is found to consist only of the outer yellow layer. The inner brown layer, prominent in the hyperplastic adrenal gland, is so thin as to be scarcely recognizable.

No adrenal tumor has been encountered in a rest of cortical tissue outside the capsule of one or other adrenal gland. The possibility of such an ectopic adrenocortical tumor must be kept in mind, however, for theoretically it can occur. In our early cases caused by what we now believe to be true adrenocortical hyperplasia, we made a thorough search of the entire retroperitoneal area for such a neoplasm in accessory tissue. None was found. Since we now believe that we can recognize adrenocortical hyperplasia grossly at the operating table, such a search is no longer carried out, for the presence of hyperplasia excludes a hyperfunctioning tumor. Any accessory cortical tissue would also be hyperplastic and presumably only in small pieces comparable to those encountered close to the kidney and adrenal glands.

Gonads. The ovaries of the first 10 women were examined at the initial adrenal operation. Gross ovarian atrophy was found. We have been unable to diagnose a comparable atrophy of the testes; no biopsies have been made.

Thymus. Thymic tumors have been reported in an occasional patient exhibiting Cushing's syndrome. The first report coming to our attention was that of Leyton, Turnbull and Bratton,[27] in 1931. Because of that report we have examined every patient for evidence of a thymic tumor. In the early years, when we were uncertain of the glandular etiology of this disease, we even went so far as to give therapeutic irradiation to the thymic region in 1 patient (Case 2). This resulted in no benefit. In none of our patients has there been roentgenographic or autopsy evidence of a thymic enlargement. Since the 2 cases reported by Leyton, Turnbull, and Bratton[27] we have become aware of 6 additional cases. Two of these have been reported,[28,29] and we have been told of the other 4 by personal communication.[30,31*]

*Shelton[31] has told us of a case similar to Turnbull's, a patient with the classic findings of Cushing's syndrome with a large mediastinal tumor, possibly of thymic origin.

When thymic enlargement is considered, possible carcinoma of the lung must be kept in mind. Brown[32] reported an oat-cell carcinoma of the lung in a patient with undoubted Cushing's disease. Mach[33] has told us of a second patient. One of our cases (Case 36) was found at post-mortem examination to have such a lesion, and Olivecrona[34] has informed us of a fourth.

Thyroid gland. In patients coming to autopsy the gross and microscopic appearance of the thyroid gland has been within the limits of normal. The suppression of thyroid function, however, suggests that there may be some atrophy of the gland not recognizable grossly or microscopically (this question of thyroid function is discussed at greater length below, in the section on Laboratory Findings).

Pancreas, parathyroid glands, posterior pituitary gland and pineal gland. In spite of the disturbance of carbohydrate balance common to patients with Cushing's disease, no anatomic abnormality has been proved in the pancreas in our cases. At autopsy in one Albright and MacMahon[16] found an increased number of enlarged islands of Langerhans with mitotic figures. No other similar finding has been encountered in this series or described in the literature. Similarly, although osteoporosis is one of the characteristics of Cushing's syndrome, no anatomic abnormality of the parathyroid glands has been found although our pathologists have looked assiduously for this. The glands have been normal without evidence of primary or secondary hyperplasia or tumor.

Nothing has been determined about possible pathologic changes of the posterior pituitary and pineal glands. The possibility of disease in these glands should be kept in mind since in Cushing's disease there is disturbance of water and electrolyte metabolism and of sexual function.

Laboratory Findings

Overabundance of the hormones of the adrenal cortex brings about profound changes in physiologic function. Those changes that can now be demonstrated presumably represent only a portion of the processes of the disease.

The blood pressure is commonly elevated in Cushing's syndrome. In our 46 patients there were 8 whose blood pressure did not exceed 150 systolic, 95 diastolic. Moderate elevation with variability of blood pressure was the rule, and severe elevation was encountered in only a few. The mechanism of the blood-pressure elevation is not understood; we have seen it disappear within a few days of adrenalectomy in several cases. This indicates hormonal component in its causation.

A tendency to glycosuria and an elevated blood sugar level has been encountered. The majority of our patients have had a normal fasting blood sugar; only 4 of 46 had a fasting level above 150 mg. per 100 cc. Frequently, they demonstrate an inability to

maintain a normal blood sugar in the face of ingested carbohydrate as measured in a glucose tolerance test. Twenty-nine of 35 had a diabetic type of sugar curve. Ten of 17 tested were insensitive to the administration of insulin.

The urinary excretion of 17-ketosteroids varied widely; it tended to parallel the degree of virilism. Significant elevation of the 17-ketosteroid excretion was seen more commonly in the cases of malignant adrenal tumor and in the cases of hyperplasia.[35] In the 4 patients with malignant tumors in whom the estimation was made, the 17-ketosteroid excretion was elevated to three or four times the normal level. In 22 of the 27 patients with hyperplasia in whom it was measured the excretion was elevated — in 9 to levels comparable to those with malignant tumors. Only 2 of the 10 patients with benign adenoma in whom the measurement was made had an elevation of urinary 17-ketosteroids.

The urinary excretion of corticosteroids or steroids with an oxygen atom in the eleventh position of the steroid molecule is probably elevated more constantly in Cushing's syndrome. The steroids of this type are thought to be the direct measure of the secretion by the adrenal cortex of steroids including compounds E and F responsible for the dominant characteristics of the syndrome. Methods of analysis for these steroids are less satisfactory than those for 17-ketosteroids, and they have been evolving during the period of observation of these patients. Seventeen patients had analysis of urinary excretion of these steroids by one or more methods.[36-38]; 15 were found to have elevated excretion. The order of magnitude is so small that metabolic studies have not been able to demonstrate it.

Patients are presumably in negative nitrogen and negative potassium balance.[7] In contrast the patients tend to conserve sodium and on a high-sodium diet may suffer sodium overloading and edema. Because of the established sodium loss and low serum level in Addison's disease[39] we had anticipated a greater derangement of sodium metabolism in Cushing's disease. We have explored the sodium question further by measuring the sodium space with radioactive sodium in 5 patients. It was found to be within the normal range and the same size both before and after adrenalectomy with correction of the disease.

The calcium balance is almost always negative, and this is largely caused by an increased excretion in the urine.[40-42]

These abnormalities of the metabolism of electrolytes are reflected in the hypokalemic alkalosis and the osteoporosis seen in many fully developed cases of Cushing's syndrome. A high serum carbon dioxide content (greater than 28 milliequiv. per liter) is a frequent finding. It was present in 37 of 43 patients in whom the determination was made. A low serum potassium (less than 3.5 milliequiv. per liter) is less commonly encountered; it was present in 13 of 141 patients in whom it was measured. The serum levels of sodium, chloride, calcium, phosphorus and phosphatase were within normal limits.

There is suggestive evidence that the level of thyroid function is depressed in Cushing's syndrome.[43] The evidence for this in the patients of this series is equivocal. The basal metabolic rate is usually in the range of −15 to −25 per cent; it was −11 per cent or below in 16 of 25 patients and normal in the other 9. The protein-bound iodine level, measured in 7 patients who had not had an intravenous pyelogram previously, was normal. The forty-eight-hour uptake of radioactive iodine by the thyroid gland ranged from 26 per cent to 49 per cent in 7 patients who had received no iodine previously. These uptakes are in the accepted normal range.[44]

No adequate technics are yet available for direct measurement of anterior pituitary function; therefore, the physiologic role of this gland in Cushing's disease remains a matter of speculation.

(To be concluded)

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UPTAKE AND BLOOD LEVEL OF RADIOACTIVE IODINE IN HYPERTHYROIDISM*

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THE most widely applied technic involving the use of radioactive iodine in the diagnosis of hyperthyroidism is the measurement of the thyroid uptake after the oral administration of tracer doses. The size of the tracer and the time at which the uptake is measured have been varied by individual observers. Most determinations, however, are made at twenty-four hours after the tracer dose even though in some patients maximum accumulation will not have occurred at that time, whereas in others the peak uptake may have taken place at an earlier period. In spite of these limitations the measurement of the twenty-four-hour uptake has proved useful and has received widespread acceptance.

However, everyone who has worked with this method has been impressed by the fact that there is no sharp dividing line between the uptake in normal subjects and that in those suffering from active hyperthyroidism. It is generally accepted that uptakes of less than 50 per cent of the tracer dose are found in nontoxic patients and that values above this level are indicative, if not diagnostic, of hyperthyroidism. At this level, however, there is a significant degree of overlap between normal and hyperthyroid subjects that impairs the diagnostic usefulness of the method.

In an attempt to devise a diagnostic method of greater specificity the determination of the plasma levels of protein-bound I^{131} after the administration of tracer doses was introduced in 1950[1] and expanded in 1952.[2] This method has been demonstrated to be of distinct value, and it is the purpose of this paper to present data on the comparative usefulness of the two procedures here discussed—namely, twenty-four-hour uptake by the thyroid gland and plasma levels of protein-bound I^{131} after tracer doses.

MATERIAL

Five hundred consecutive patients referred to the Thyroid Group of the departments of Medicine and Physics of the Mount Sinai Hospital were selected for study. Only patients who had had no previous treatment directed to their thyroid glands were included. Care was taken to scrutinize all patients who had received medication known to affect either thyroid function or the results of studies with I^{131}. No patients with previous hyperthyroidism treated by surgery, irradiation, antithyroid drugs or radioactive iodine were included. If patients had received stable iodine medication in any form, they were excluded or a sufficient period was allowed to elapse to ensure that all effects of these medications had disappeared. Before the I^{131} studies were carried out the patients were classified clinically as normal (euthyroid) or hyperthyroid by at least two physicians specially trained in thyroid diseases. The classification was based on a complete history and physical examination supplemented when necessary by such laboratory aids as the basal metabolic rate, the blood cholesterol and the protein-bound iodine of the serum. The group selected consisted of 96 hyperthyroid and 404 euthyroid patients. Each of these patients was given a tracer dose of I^{131}.‖ The uptake by the thyroid gland was measured at twenty-four hours, and the level of the plasma protein-bound I^{131} was determined at seventy-two hours after the tracer dose.

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‖Supplied on allocation by the United States Atomic Energy Commission.

Methods

I^{131} Uptake

A dose of 25 to 100 microcuries of carrier-free I^{131} is administered by mouth in about 100 cc. of water. The number of microcuries present in the thyroid gland is measured twenty-four hours later, a properly shielded bismuth Geiger–Müller tube at a distance of 23 cm. from the jugular notch being used. This tube was previously calibrated with the use of sources of I^{131} of known concentrations at the same working distance. The uptake is recorded as the percentage of the administered dose present in the thyroid gland, allowing for decay.

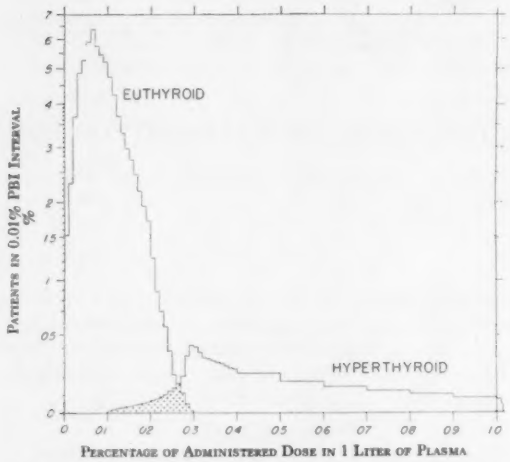

Figure 1. *Frequency Distribution of 500 Patients for Protein-Bound Plasma I^{131}.*

Twenty-six hyperthyroid patients, corresponding to 5 per cent of the total, who had a level above 1 per cent are not plotted. Critical diagnostic value is 0.26 to 0.27 per cent. Dotted area indicates diagnostic errors (1.6 per cent of all patients).

I^{131} Blood Levels (Method of Silver et al.[3])

Seventy-two hours after the administration of the same tracer dose that was used for the uptake studies, venous blood is drawn, and 4 cc. of serum or plasma is pipetted into a test tube 15 x 125 mm. This is placed in a well-type crystal scintillation counter,* and the radioactivity is measured, the instrument having previously been standardized with known concentrations of I^{131} in the anticipated range. If the reading of this 4-cc. sample is less than 0.00027 per cent of the administered dose per cubic centimeter (0.27 per cent of the administered dose per liter of plasma) no further determination is required, and the value is in the euthyroid range. If the value for the untreated serum (or plasma) is 0.27 per cent or higher, it is necessary to determine the protein-bound I^{131} (as distinguished from the total I^{131}, which represents inorganic I^{131} in the form of iodide and protein-bound I^{131} in a form presumably hormonal). To the 4 cc. of plasma in the test tube previously measured is added approximately 11 cc. of 10 per cent trichloroacetic acid. This is well mixed and then centrifuged. The supernatant fluid is discarded, and the precipitate is resuspended in 12 cc. of 3 per cent trichloroacetic acid, well mixed and again centrifuged. This supernatant is discarded, and the precipitate washed again as before. The final supernatant is again discarded, and the final precipitate is dissolved in 4 cc. of 8 per cent sodium hydroxide. The tube is then replaced in the well counter, and the radioactivity of its contents recorded. Three washings, properly performed, will remove all inorganic I^{131} likely to be encountered. The upper limit of normal for protein-bound I^{131} is 0.27 per cent of the administered dose per liter of plasma (or serum) at seventy-two hours after the tracer dose. Values above this are considered "hyperthyroid."

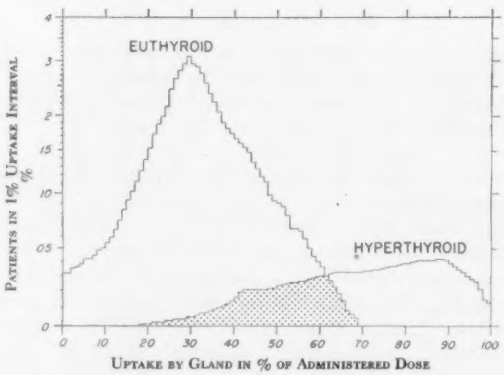

Figure 2. *Frequency Distribution of 500 Patients for I^{131} Uptake by the Thyroid Gland.*

Critical diagnostic value is 61 per cent. Dotted area indicates diagnostic errors (7.2 per cent of all patients).

The 4-cc. sample of plasma here recommended is used when the tracer dose is approximately 25 microcuries of I^{131}. If the tracer dose approaches 100 microcuries, only 1 cc. of plasma is necessary for the determination.

It is important that all apparatus used in this procedure be kept specifically for this purpose and never be used for tracer or therapeutic doses of I^{131}. Unless this is done the problem of decontamination is almost insoluble.

Results

The results obtained in these 500 patients are shown in Figures 1 and 2. Inspection of Figure 1 shows a sharp peak in the distribution of the values for the protein-bound I^{131} of the plasma in euthyroid subjects and little overlap between the values obtained in normal and in thyrotoxic patients. Inspection of the

*If no well-type scintillation counter is available the methods outlined in previous communications[1,2] can be followed. We now use a well-type scintillation counter exclusively.

uptake studies (Fig. 2) shows more spread in the distribution of values obtained in normal patients, with considerable overlap between the toxic and nontoxic cases.

Statistical Examination of Results

Protein-bound radioactive-iodine levels of plasma. Figure 1 represents the frequency distribution of 404 euthyroid and 96 hyperthyroid patients plotted against protein-bound I^{131} in percentage of administered dose per liter of plasma.* There is an overlap of the two curves in the region of 0.1 to 0.3 per cent, and a critical value must be defined somewhere within this range below which patients may be considered euthyroid and above which they may be considered hyperthyroid. We shall select this critical value in such a way that the number of patients improperly classified on the basis of this criterion is minimized. It can be shown that this condition is met if the protein-bound I^{131} value is selected that corresponds to the intersection of the two frequency distributions, 0.26 to 0.27 per cent. The number of patients in the wrong classification, represented by the dotted area, is equal to 1.6 per cent of the cases. In terms of the rough data this means that 4 hyperthyroid patients were classified as euthyroid and 4 euthyroid ones as hyperthyroid. The frequency of error appears at first glance to be extremely low. It must be considered, however, that in our sample there were only 20 per cent hyperthyroid patients, so that our worst diagnostic error, if we were to consider every patient euthyroid, would have amounted to 20 per cent. This worst error is reduced to 1.6 per cent, or by a factor of 12.

Uptake of I^{131} in the thyroid gland. The frequency distribution of I^{131} uptake by the thyroid gland in percentage of the administered tracer dose is shown in Figure 2. The critical value of uptake to be used as a diagnostic criterion can be derived here in the same way as that for protein-bound I^{131}, and it corresponds to an uptake of 61 per cent. The errors, which are again represented by the dotted area, amount to 7.2 per cent, or to 5 euthyroid patients classified as hyperthyroid and 31 hyperthyroid patients classified as euthyroid. This result is much less satisfactory than that with protein-bound I^{131} since it is a reduction of the worst error of 20 per cent by a factor less than 3.

It may not be obvious that the selected critical value of 61 per cent is the best one since this value is higher than the one commonly used and since it gives more errors among the hyperthyroid than among the euthyroid patients, with a total of 36 errors. An equal number of diagnostic errors in the two groups is obtained for a critical value of 55 per cent. In this case there are 22 euthyroid and 22 hyperthyroid patients incorrectly classified, or a total of 44 diagnostic errors. This corresponds to 8.8 per cent of all cases, compared to 7.2 per cent for a critical value of 61 per cent uptake.

It may be desirable to select, instead of a single critical value, a critical or diagnostic range for uptake and to consider patients within this range as unclassified. The selection of such a range depends on the

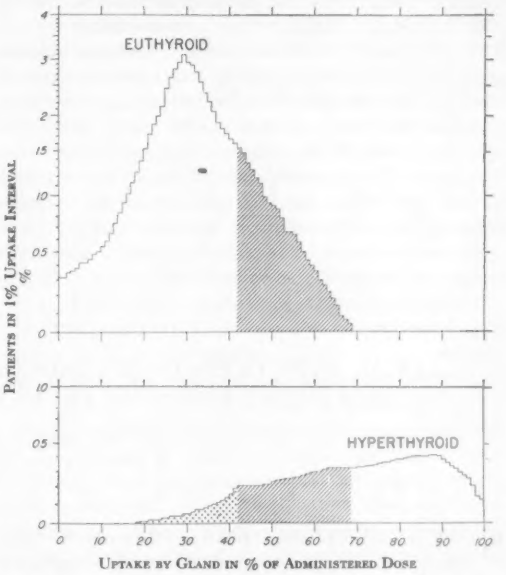

FIGURE 3. *Frequency Distribution of 500 Patients for I^{131} Uptake by the Thyroid Gland, Showing the Use of a Diagnostic Range of 42 to 69 Per Cent.*
The dotted area indicates diagnostic errors (1.6 per cent), and the crosshatched areas the unclassified cases (25 per cent of all patients).

percentage of diagnostic errors in classification that one is willing to accept. If these errors are to be limited to the same percentage as that with protein-bound I^{131} — that is, to about 1.6 per cent — a critical range with a minimum number of unclassified patients should be selected. Figure 3 presents the result of such a selection of a range between 42 and 69 per cent uptake. Twenty-five per cent of all patients are unclassified (90 euthyroid and 37 hyperthyroid patients), and 1.6 per cent have a wrong classification (7 hyperthyroid patients are classified as euthyroid and 1 euthyroid patient is classified as hyperthyroid).

It should be noted that the frequency data obtained by interpolation were used only to determine the critical diagnostic values and the critical range but that the errors mentioned in the discussion, both in percentage and in the indicated numbers of patients, are the actual figures obtained by application of the derived critical values to the rough data.

Summary and Conclusions

A series of 96 untreated hyperthyroid patients and 404 normal subjects was studied with radioactive-

*To obtain a better interpolation the rough data were plotted as a cumulative frequency graph; this was interpolated in a smooth curve. The frequency distributions in the illustrations were obtained by graphic differentiation of the interpolated cumulative frequency curve.

iodine diagnostic technics. The thyroid uptake at twenty-four hours after the tracer dose and the blood plasma levels of protein-bound I^{131} at seventy-two hours after the tracer dose were determined in each patient.

It was found that uptake studies were not as accurate a diagnostic method as the levels of protein-bound I^{131} at seventy-two hours after the tracer dose.

If a critical value for the protein-bound I^{131} of 0.27 per cent of the administered dose per liter of plasma is taken, there were 8 diagnostic errors as a result of this determination, or 1.6 per cent errors in classification. At a critical uptake value of 61 per cent there were 36 diagnostic errors, or 7.2 per cent. To reduce the diagnostic error of the uptake method to that attained by the determination of the protein-bound I^{131} (1.6 per cent) it was necessary to select a critical *range* rather than a critical *value*. This range was an uptake between 42 per cent and 69 per cent. If only uptakes below 42 per cent are used to diagnose the euthyroid state and values above 69 per cent are used to diagnose hyperthyroidism the total diagnostic error will be the same as that obtained by the protein-bound I^{131} method — namely, 1.6 per cent. The use of this "diagnostic range," however, leaves 127 patients, or 25 per cent of the entire series, unclassified by this method, whereas the protein-bound I^{131} method attains the same accuracy with no unclassified cases.

We are indebted to Dr. Josephine K. Mayer and Mrs. Marta Fried for technical assistance.

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LOCAL INJECTIONS OF HYDROCORTISONE AS A NEW AND EFFECTIVE TREATMENT FOR STRICTURES OF THE URETHRA AND MEATUS*

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STRICTURES of the human urethra are of three types: inflammatory, traumatic and congenital. The basic histology[1] common to all strictures is a proliferation of fibroblasts in the tunica propria. This progresses to the point where the elastic tissue and muscle fibers of this area are destroyed and replaced by fibroblasts. In extreme cases the mucosa and corpus spongiosum are also replaced. In inflammatory strictures, the proliferation is accompanied by a marked infiltration of leukocytes. This infiltration takes place to a much less degree in traumatic strictures and is entirely absent in congenital strictures.

The clinical course, treatment, complications and prognosis of all types of strictures are similar and in many cases have been quite discouraging.

Strictures of the anterior and posterior urethra are noticeably resistant to treatment and usually require months to years of continuous therapy. Over a long period, with the use of the common methods of treatment, which include simple dilatation with sounds, filiform dilatation and internal or external urethrotomy,[2] most of these strictures are said to be cured. Nevertheless, many urologists hold that strictures are never actually cured and that occasional passage of a full-size sound is imperative for prophylaxis.[3]

Other methods, including complicated surgical procedures, have also been attempted but have failed to demonstrate dramatic or consistently good results. Davis and Lee[4] performed internal urethrotomy in 45 cases of urethral stricture. Of 36 patients followed for four to forty months, 29 reported a satisfactory urinary stream. However, no record of calibrations was made in these patients, and 7 of them continued to require interval dilatation. It is also stated in the discussion of this report that postoperative strictures, such as those after transurethral prostatectomy, become very troublesome and resistant to any form of therapy.

Scardino and Hudson[5] used tocopherol in the treatment of urethral strictures, because of the favorable results reported in cases of Peyronie's disease and fibrositis. Of 22 patients who received 200 to 1200 mg. of mixed tocopherol daily, the results were good in 15, fair in 4 and negative in 3. This is a very expensive form of therapy and is far too costly for many patients.

Angle and Pfeifer[6] treated 6 cases of urethral stricture by bold excision with a small resectoscope. This was done in patients who did not respond to the usual dilatation with sounds. Five of these patients showed satisfactory results.

More recently, Reid and Moore[7] have reported on a new method of treating these strictures. Previously,

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they had dilated strictures maximally under anesthesia and had left an indwelling catheter in place for two days. Patients were then discharged without catheter to the outpatient department, and often the caliber of the stricture returned from a No. 24 French to a No. 16 French in an interval of one week. In the new method the urethra is dilated, and a small catheter is left in place. It is replaced with catheters of progressively larger size at intervals of two to four days until the desired caliber is obtained.

Meatal strictures frequently follow endoscopic prostatic resection,[8] and their rate of occurrence is said to be increasing.[9]

The chronicity of these strictures and the difficulty of treating them by simple dilatation with sounds are attested by Landes,[10] who states that, even with liberal meatotomy before operation, approximately every fifth patient who undergoes transurethral resection of the prostate will have a greater or lesser meatal stricture at the time of the first postoperative visit. Some of these strictures are mild, soft and easily dilatable, and others are severe to the point of complete obstruction, induration and resistance. Nesbit et al.[11] state that in certain difficult cases Z-plasty is required to solve this problem.

The preceding discussion makes it evident that a simple, inexpensive, effective therapy for urethral and meatal strictures would be most useful for those who suffer from this disability.

The treatment of meatal and urethral strictures reported in this paper was the outgrowth of observations made by one of us (C.D.B.) of the resolving effect of hydrocortisone injected into scar and fibrous tissue such as is seen in retracted tendons of spastic hemiplegic and paraplegic patients. The introduction of an anti-inflammatory agent such as hydrocortisone into strictures of the urethra was considered even more worthy of trial after review of a number of reports in the literature regarding the apparent lysis of fibrous tissue by this agent.

As early as 1950 the effect of cortisone and hydrocortisone on connective tissues was studied. At this time Ragan[12] reported that, in wounds of animals treated with ACTH or cortisone, fibroplasia, capillary growth and ground-system proliferation were depressed; although these wounds ultimately healed, there was a considerable delay as compared to the controls. Scheinberg and Saltzstein[13] reported that in a series of Mann–Williamson dogs treated with cortisone and killed several weeks later, there was a marked reduction in the number and extent of intra-abdominal adhesions as compared to the controls. This stimulated further investigation, and adhesions were created in 30 dogs by sprinkling talc evenly over one side of the serosal surface of the small bowel. In all control animals the small bowel was a dense mass of adherent loops, whereas cortisone-treated animals showed transparent, thin serosa with loops easily removed from the body. Johnson et al.,[14] because of the lack of abdominal adhesions discussed above, decided to evaluate the effect of cortisone on experimentally produced myocardial infarcts in dogs. There was a definite decrease in local fibroblastic proliferation. During the early stages of healing, direct action on the vascular system of the heart was also noted with the appearance of an increased number of interarterial anastomoses in the myocardium.

Two other groups of investigators[15,16] studied the same problem but were unable to reproduce these results. Byrne[17] treated 31 patients with urethral strictures with cortisone by the oral route in a dosage of 300 mg. in the first twenty-four hours and 100 mg. daily for the next thirty days. All patients were hospitalized for the first three days while dilatation was done under anesthesia, and an indwelling No. 24 French Foley catheter was inserted after extreme dilatation and was permitted to remain as a splint for three days. This procedure, of course, is an approved method of treatment of strictures without the use of cortisone. In 17 of Byrne's cases encouragingly good results were obtained. Baker et al.[18] administered cortisone orally to dogs and then to patients after ureterointestinal anastomoses. They reported a significant reduction in secondary stricture formation in the presence of infection. This reduction of connective-tissue hyperplasia was not seen, however, in reanastomoses of ureters to bladders when infection was absent. These writers believed that cortisone had no effect on fibroplasia in the uninfected healing wound. Furthermore, hydrocortisone has been injected locally into the fibrous-tissue plaques of Peyronie's disease with good results. In 1 patient the fibrous plaque disappeared completely after three injections of 25 mg. each.[19]

Method of Injection

Ten patients with meatal and 8 with urethral strictures are included in this study. Before treatment, with the aid of such standard urologic instruments as metal sounds, filiforms and followers and of bougies à boule, the "size" of the urethra at the site of the stricture was measured without overdistention, and the calibration was expressed in terms of the usual "French" size as used by urologists.

An aqueous suspension of hydrocortisone was injected directly into the stricture at two clock positions—5 and 7 or 3 and 9. In the meatal stricture no anesthesia was required, and the injection was done directly without the aid of urethroscopy, a 2-cc. syringe and a 22-gauge needle being used.

Strictures of the anterior and posterior urethra were located and visualized through the McCarthy foroblique panendoscope, and injection was done with an endoscopic needle passed through the panendoscope and inserted into the stricture under direct vision. The most important feature of this insertion was to get the needle well under the mucosa and into the tunica propria before the hydrocorti-

sone was injected. This injection was done under local intraurethral anesthesia with 1:500 Nupercaine solution or under spinal anesthesia or general anesthesia as the case indicated. With each treatment the stricture was first dilated to its limit of distensibility *without* rupture.

Initially, 6.25 mg. of hydrocortisone was injected into each of the two sites mentioned, three times on alternate days. Later, the dose was increased to 12.5 mg., and the number of injections as well as the interval between them was varied to suit the individual case. All patients received prophylactic chemotherapy during cortisone administration.

TABLE 1. *Summary of Results.*

Case No.	Patient	Age	Sex	Site of Stricture	Cause	Duration of Stricture	No. of Injections	Total Dose
		yr.						mg.
1	G.C.	56	M	Meatus	Transurethral resection	(New)	3	37.5
2	H.T.	36	M	Anterior urethra*	Gonorrhea	10 yr.	3	37.5
3	H.J.	72	M	Meatus	Transurethral resection	(New)	8	137.5
4	B.B.	42	M	Posterior urethra	Gonorrhea	25 yr.	3	37.5
5	W.E.	60	M	Meatus	Transurethral resection	(New)	2	50.0
6	H.H.	70	M	Anterior urethra	Gonorrhea	(Newly discovered)	2	25.0
7	P.S.	28	M	Anterior urethra	Traumatic	8 yr.	5	137.5
8	M.M.	65	M	Anterior urethra	Gonorrhea	2 mo.	1	25.0
9	V.P.	49	M	Anterior urethra	Gonorrhea	11 yr.	2	50.0
10	D.J.	66	M	Anterior urethra	Traumatic	3 yr.	3	75.0
11	M.M.	53	F	Meatus	Inflammatory	2 yr.	3	50.0
12	S.L.	74	M	Anterior urethra	Gonorrhea	3 yr.	1	25.0
13	G.N.	17	M	Meatus	Transurethral resection	3 yr.	3	75.0
14	S.T.	62	M	Meatus	Transurethral resection	(New)	2	50.0
15	E.C.	82	M	Meatus	Transurethral resection	(New)	3	75.0
16	F.W.	67	M	Meatus	Transurethral resection	(New)	2	50.0
17	H.K.	58	M	Meatus	Transurethral resection	(New)	3	75.0
18	J.M.L.	84	M	Meatus	Transurethral resection	(New)	2	50.0

*Strictures of membranous as well as pendulous penile urethra.

Results

All pertinent data are summarized in Table 1. Even by the most conservative standards, results were excellent in all patients. Only 1 of the 18 patients in this series required a second single dilatation after treatment. Three representative case histories are summarized below.

Case 1. A 56-year-old man, the 1st patient treated, had a transurethral resection of the prostate gland in November, 1953. Several weeks later a stricture of the meatus developed and was calibrated at No. 20 French. On December 14, 6.25 mg. of hydrocortisone was injected into 2 sites at the base of the stricture. Two urologists examined the patient and predicted that he would need a meatotomy. On December 16 the meatus could be dilated easily to No. 26 French, and the stricture was much softer on palpation. The injection was repeated. Two days later the stricture was almost nonexistent; the sounds dropped into position up to No. 26 French, and the 3d and last injection was given. At each subsequent follow-up examination no stricture was demonstrable, and the size of the meatus remained consistently at No. 26 French.

The most striking observation in this case was the softness and distensibility of the stricture after the first injection. This impression has been maintained. This stricture, predicted to require many dilatations and possible meatotomy, disappeared after three injections and 2 dilatations. All meatal strictures in this series responded equally well except for 1 patient (Case 3), who had a more stubborn stricture and required 8 injections. It was this experience that led to the administration of increased amounts of hydrocortisone to subsequent patients.

Case 2. A 36-year-old man contracted gonorrhea at the age of 25, after which a stricture of the anterior urethra developed just distal to the external sphincter. At first dilatations were necessary at 4-week intervals. As the years passed this stricture became markedly fibrous, and dilatations had to be carried out every other week. The passage of the sound was accomplished with more and more difficulty, and a filiform catheter with followers had to be used. On February 3, 1954, 6.25 mg. of hydrocortisone solution was injected into 2 sites in the stricture, which was dilated with difficulty to No. 24 French. Two days later the stricture

calibrated easily at No. 24 French and was strikingly and easily distensible. Another injection of the same amount of hydrocortisone was given. The urinary symptoms disappeared, and the patient felt so well that he failed to keep his next appointments. On February 24 he returned for his final injection. A No. 24 French catheter was easily passed, and the stricture was no longer present. This caliber has been maintained, and the patient has been symptom free since that time.

The previous observations of immediate softness and easy distensibility noted in the fresh meatal stricture also held true for this old, tough inflammatory stricture of the urethra. Similar results were obtained in all urethral strictures, sometimes with only 1 injection. Only 1 patient required a second dilatation; this case is described below.

Case 10. This patient was a 66-year-old man whose urologic problem was the original stimulus to the investigation of this method of therapy. He had had a suprapubic prostatectomy in 1947. This was followed in 1949 by local resection of a bladder carcinoma and the implantation of radon. Subsequently, he required many cystoscopies, and a stricture developed in the anterior urethra that was dilated with difficulty every 24 days. On June 16, 1954, the urethra was calibrated at No. 18 French and was dilated with difficulty to No. 28 French for cystoscopy and additional radon implantation. Three days later the stricture had narrowed to No. 22 French and was redilated with difficulty to No. 28 French after the injection of 12.5 mg. of hydrocortisone at 2 sites. Two days later the stricture was soft, and the urethra was easily dilated to No. 30 French. A 2d treatment was given. On June 23 the stricture was no longer noticeable, and the urethra was still calibrated at No. 30 French. After a 3d injection the patient did well for a month, at the end of which complete urinary obstruction developed. A local urologist passed sounds easily and found no clinical evidence of stricture; however, a piece of eschar from the site of radon implantation was floating loosely in the bladder and had occluded the urethra. Removal of this corrected the urinary obstruction. About 9 weeks after treatment the patient noted that his urinary stream was slowing and returned for a dilatation. This was accomplished with ease by the urologist, who could not be certain that a constriction had taken place. Since that time the patient has been seen at intervals for checkups of his bladder cancer, and all cystoscopies have been done in the urologist's office through an adequate urethral passage, whereas hospitalization and spinal or Pentothal anesthesia were formerly required.

Table 1 *(Concluded).*

Case No.	Caliber of Stricture		Frequency of Dilatation		Duration of Follow-up Study	Result	Remarks
	Before therapy	After therapy	Before therapy	After therapy			
					mo.		
1	No. 20 French	No. 26 French	None	0	14	Excellent	No clinical evidence of stricture
2	Filiform	No. 24 French	Every 2 to 4 wk.	0	12	Excellent	No clinical evidence of stricture
3	No. 16 French	No. 26 French	None	0	12	Excellent	No clinical evidence of stricture
4	Filiform	No. 26 French	Weekly	0	12	Excellent	Therapy followed internal urethrotomy; catheter left in urethra for 2 days before operation.
5	No. 16 French	No. 26 French	None	0	11	Excellent	No clinical evidence of stricture
6	Filiform	No. 26 French	None	0	9	Excellent	No clinical evidence of stricture
7	No. 16 French	No. 26 French	Every 2 to 6 wk.	0	9	Excellent	Stricture developed after repair of hypospadias with mucosal graft; no clinical evidence of stricture.
8	Filiform	No. 26 French	Weekly	0	8	Excellent	No clinical evidence of stricture
9	Filiform	No. 24 French	Every 2 wk.	0	8	Excellent	No clinical evidence of stricture
10	No. 18 French	No. 30 French	Every 24 days	1	8	Excellent	One dilatation done because patient thought urinary stream slowing up; sound inserted easily, & stricture soft.
11	No. 18 French	No. 28 French	Every 2 to 4 wk.	0	8	Excellent	No clinical evidence of stricture
12	Filiform	No. 22 French	Every 2 to 12 wk.	0	8	Excellent	No clinical evidence of stricture
13	Filiform	No. 26 French	None	0	6	Excellent	No clinical evidence of stricture
14	No. 14 French	No. 26 French	None	0	5	Excellent	No clinical evidence of stricture
15	No. 12 French	No. 26 French	None	0	5	Excellent	No clinical evidence of stricture
16	No. 14 French	No. 24 French	None	0	5	Excellent	No clinical evidence of stricture
17	Filiform	No. 26 French	Every 2 wk.	0	5	Excellent	No clinical evidence of stricture
18	No. 16 French	No. 24 French	None	0	4	Excellent	No clinical evidence of stricture

This result may be considered excellent in spite of the 1 additional dilatation. This therapy has saved the patient discomfort, time and hospitalization expense since it has made it possible for cystoscopy to be carried out in the urologist's office.

Discussion

The therapy described above, if judged by the 18 patients treated in this preliminary study, meets the requirements of an effective regimen for the control of meatal and urethral strictures. It is simple and relatively inexpensive, can be completed in a short time and so far has proved completely effective.

The average number of injections needed was 3,

but good results were at times obtained with 1 or 2. Only 2 patients require more than 3 injections (5 and 8 respectively). Success of therapy did not appear to depend on the duration of the stricture, since a definite change occurred in every case after the first injection. This was a softening and an easy distensibility that progressed to the point where a stricture could no longer be felt. These results seem to have been maintained, since these patients have been followed for four to fourteen months without change in the clinical picture.

It is obviously difficult to prove the disappearance of these strictures by pathological studies. Further experiments are under way to investigate the mechanisms of this phenomenon by the creation of urethral strictures in animals, and the study of the pathology of this area.

The implications of this form of treatment in the field of genitourinary surgery are far reaching. It is believed that the effectiveness of hydrocortisone injected locally into urethral and meatal strictures has been well enough demonstrated so that one of us (M.K.L.) now uses it prophylactically at the time of transurethral surgery to prevent meatal strictures.

The problem of vesical-neck contracture and fibrosis is one that may plague the urologist with the chronicity and recurrence of these conditions. Here, too, there is a place for further investigation of the use of locally injected hydrocortisone, both as adjuvant therapy and as a prophylactic measure. Preliminary work has already started in this direction. Furthermore, the use of this substance may be helpful in the repair of hypospadias, in urethroplasty and possibly to prevent stricture formation in the various surgical procedures involving the ureters. Direct injection of Hunner's ulcers of the bladder also seems to be appropriate. An obvious advantage of the direct injection of hydrocortisone in contrast to oral therapy is the total absence of systemic side reactions.

Summary

Ten patients with meatal strictures and 8 patients with urethral strictures received injections of hydrocortisone into the stricture followed by dilatation. After an average of 3 injections old as well as new strictures disappeared, with concomitant relief of all symptoms. Patients have been followed for four to fourteen months with no return of stricture formation.

We are indebted to Dr. Samuel N. Vose, professor of urology, Boston University School of Medicine, for his encouragement and advice in this clinical study.

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MILIARY CALCIFICATION OF THE LUNGS AFTER TREATED MILIARY TUBERCULOSIS*

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MANY authors[1-5] reporting on disseminated pulmonary calcification have suggested that this entity represented healed miliary tuberculosis even though a history suggestive of acute miliary tuberculosis was lacking. Geever[6] studied 2 patients clinically, bacteriologically and pathologically and concluded, without bacteriologic proof, that tuberculosis was the cause. On the basis of negative tuberculin tests he assumed that tuberculoallergy was spontaneously extinguished because the tuberculous infection was completely healed or because the tests were done shortly before death from ulcerative ileitis in 1 patient and leukemia in the other.

Sutherland[7] believed that miliary calcification of the lungs was due to an oversaturation of the blood with calcium salts caused by an abnormality of metabolism.

Sayers and Meriwether[8] studied 125 cases of disseminated pulmonary calcification from among 18,000 miners in Picher, Oklahoma. Ninety per cent were born in Missouri, Oklahoma, Kansas, Arkansas and Illinois, and the majority were from rural areas or had spent several summers in the harvest fields. The authors cultured aspergillus from the sputum of a number of the patients and suggested that, in addition to healed miliary tuberculosis, a fungous infection could be the etiologic agent.

Olson, Wright and Nolan,[9] in an epidemiologic study of calcified pulmonary lesions in Ohio, considered *Ascaris lumbricoides* as a possible but unproved cause.

Recent evidence[10-13] stresses the high prevalence of pulmonary calcification of all types associated with tuberculin anergy and histoplasmin sensitivity. It is likely on the basis of known facts that histoplasmosis is the most common cause of diffuse pulmonary calcifications although it is recognized that coccidioidomycosis, silicosis and metastatic cancer can also produce such calcification.

Now that potent antituberculous therapy is available, acute miliary tuberculosis, formerly almost always fatal, can be expected to respond to treatment in approximately 90 per cent of cases. Because of this, healing of the miliary lesions can be expected to proceed to calcification in some cases. The cycle is now complete, and once again disseminated miliary calcification can at times be considered of tuberculous origin.

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Case Reports

Case 1. A 25-year-old woman was well until 2 weeks before admission to the hospital, when she began to notice malaise, anorexia and fatigue. Mild at first, these symptoms became so prostrating a few days before admission that she was unable to get out of bed. At this time she had a temperature of 102°F. associated with shaking chills. She was admitted to the hospital on May 26, 1949, when an x-ray film of the chest (Fig. 1) showed a soft bilateral miliary infiltration. A sternal-bone-marrow aspiration revealed tubercle bacilli, and on May 20 streptomycin, 1 gm. twice daily, with 12 gm. of para-aminosalicylic acid daily, was begun. By August 14 she had become asymptomatic and afebrile, and a chest roentgenogram showed considerable resolution in the previously reported miliary lesions. The remainder of the course was uneventful, and she was discharged on September 21, 1950. X-ray study on discharge showed a very fine, diffuse, stippled infiltration. Histoplasmin skin test was negative.

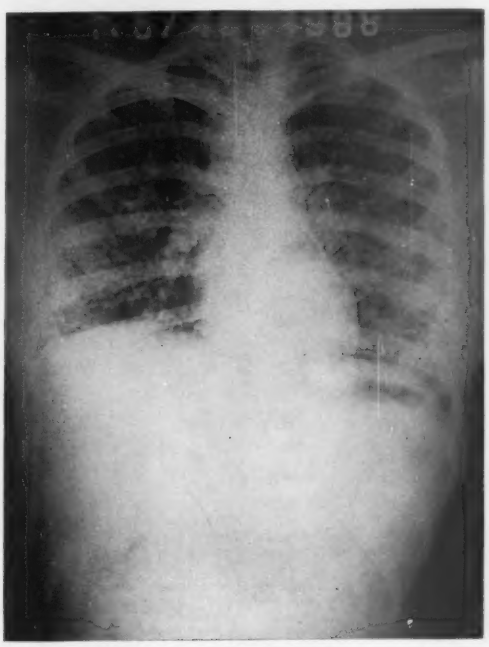


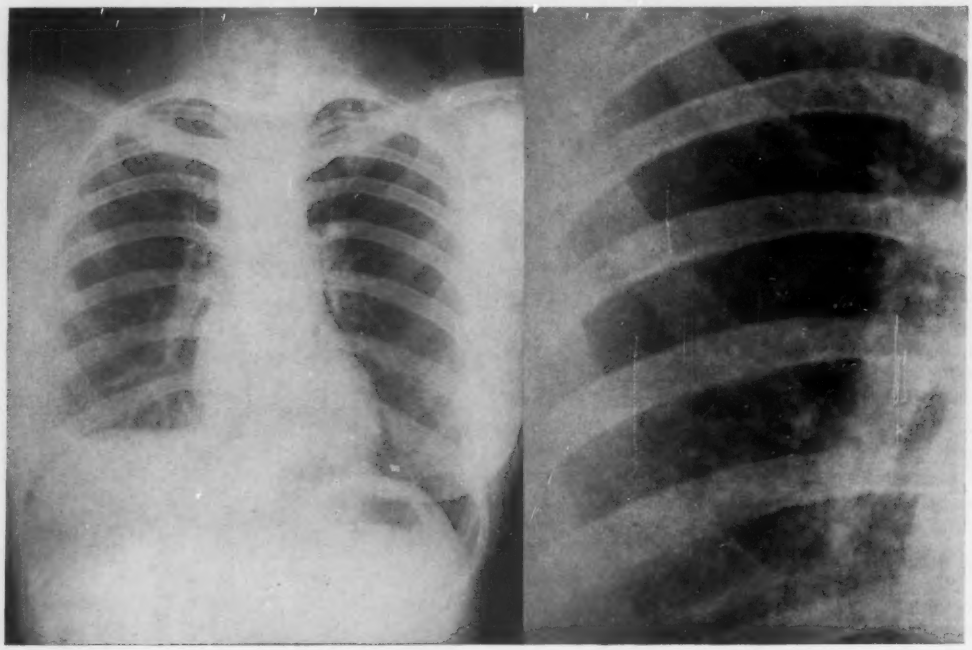
Figure 1. *Bilateral Soft Miliary Densities throughout Both Lung Fields in Case 1.*

She has remained well to date, and recent x-ray films show a diffuse firm miliary lesion, which, when examined with a hand lens, has the typical appearance of minute calcific flecks throughout both lung fields (Fig. 2*A* and *B*).

Case 2. A 28-year-old feeble-minded Negro was admitted to the District of Columbia General Hospital on March 25,

1948, his companion revealing that he had been losing weight and feeling weak and dizzy for 2 months. Three weeks before admission a temperature of 103°F., associated with night sweats and pain in the left side of the chest developed. A few days before entry he coughed up blood-streaked sputum. Physical findings revealed an acutely ill man, with a temperature of 104.6°F. and internal strabismus of the left eye, with poor reaction of the left pupil to light. There were widespread moist rales throughout the lungs, a distended, tympanitic abdomen and ++ edema of the entire left leg, with tenderness of the left femoral triangle but no redness or heat. The significant negative findings included absence of Homans's sign, lymphadenopathy and signs of meningitis. All laboratory data were negative, including a lumbar puncture and gastric, bone-marrow and sputum examinations for tubercle bacilli. X-ray study of the chest, however, showed miliary mottling of the lung fields (Fig. 3), and, because it was believed that the patient had tuberculosis, he was placed on streptomycin, 1 gm. daily, on March 26. In April tubercle bacilli were demonstrated in the gastric washings.

The course was complicated by bilateral pleural effusions, extension of the pulmonary lesions, a cold abscess of both the 6th left anterior rib and the left inguinal area. In addition, there was tuberculosis of the 10th thoracic and 1st cervical vertebras, with subluxation on the 2d cervical vertebra, resulting in a temporary quadriplegia. Immobilization and combined treatment with streptomycin and para-aminosalicylic acid resulted in firm fusion of the involved vertebras. Figure 4 shows the miliary calcification in addition to the healed extension from the original miliary process.



A B

FIGURE 2. *X-Ray Film of the Chest of the Same Patient Shown in Figure 1.*
A=*forty-two months later, showing diffuse, fine miliary lesions.*
B=*magnified reproduction, showing minute calcified nodules.*

DISCUSSION

McDermott et al.[14] first reported healing lesions in patients who died in the various stages of treated miliary tuberculosis or of its complications. In a child who died of internal hydrocephalus as a result of tuberculous meningitis (complicating miliary tuberculosis) on treatment with streptomycin for ten months, gross changes were absent in the lungs. Microscopically, however, tiny circumscribed foci of loosely arranged fibrous tissue were observed. In another case the lungs were reported to be studded with tubercles. In contrast to typical tubercles, however, these lesions consisted of three distinct pathologic zones. In the majority there was an inner zone of necrotic tissue that was surrounded by a definite ring of fibrous tissue. Beyond the zone of fibrous tissue was a ring of active cellular inflammation in which tubercle bacilli were present. Thus, it appeared as if partially healed tubercles had broken down to form newly active disease.

Roentgenographically, the appearance of various stages of miliary tuberculosis may vary between a normal chest film and one in which small, bilateral, densely uniform, calcific deposits appear, often in association with healed extension-type lesions. Lying between these two extremes will be various stages of activity and healing.

It is estimated that calcification of the type discussed takes three to five years to occur. Obviously, factors such as body resistance, rapidity and effec-

tiveness of therapy and calcium metabolism will alter this somewhat. As in Case 1 diagnosis, treatment and

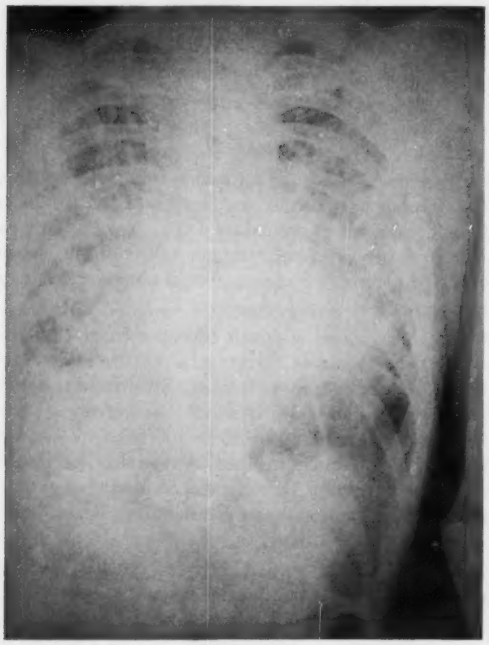


FIGURE 3. *Extensive Soft Miliary Nodules throughout Both Lung Fields in Case 2.*

recovery were prompt, and minute, barely macroscopic calcific lesions appeared forty-two months after the onset of the disease. Even though the pulmonary disease may finally stabilize, as in Case 2, this does not preclude evidence of progressive hematogenous disease in other organs of the body. Therapy in this patient was effective initially in preventing death so that in six years of hospitalization he has lived to show numerous complications in organs other than the lungs. Approximately forty months after onset of his disease, this patient began to have evidence of miliary-type pulmonary calcification.

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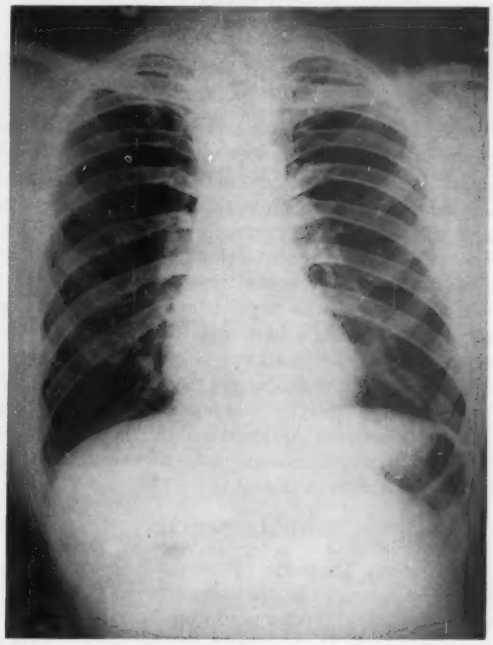

FIGURE 4. *X-Ray Film of the Chest of the Same Patient, Five Years Later, Showing Bilateral Calcified Nodules.*

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MEDICAL PROGRESS

USE OF THE DIONE DRUGS (PROPAZONE, TRIDIONE, PARADIONE, DIMEDIONE AND MALIDONE) IN THE TREATMENT OF EPILEPSY OF CHILDREN*

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THE derivatives of oxazolidine-2-4-dione have long been known, but it was not until 1941,[1] to our knowledge, that the first dione drug (Propazone) was administered to epileptic patients. Since that time four additional dione drugs (Tridione, Paradione, Dimedione and Malidone) have been synthesized and employed in the treatment of epilepsy.

The purpose of this paper is to present our results, along with those of others, with the use of these five dione drugs in the treatment of childhood epilepsy.

In discussing the efficacy of these drugs in the different types of epilepsy, it is necessary to present our distinction between petit-mal and minor motor spells, since many physicians designate all seizures of momentary duration as petit mal.

PETIT-MAL SEIZURES

We reserve the term "petit mal" for spells that consist of transient lapses of consciousness associated with bilaterally synchronous three-per-second spike and wave forms in the electroencephalogram. These attacks are encountered almost entirely in young children, particularly females, of high or at least average intelligence, between four and eight years of age. They rarely make their initial appearance after the onset of puberty.

MINOR MOTOR SEIZURES

These attacks generally make their initial appearance early in life, usually between three and twelve months of age.

Akinetic Type

When the child is in the sitting position, this type of spell consists of a sudden nod or dropping of the head, usually forward.

In the older child, who is able to stand, it consists of an abrupt loss of all muscle control that results in a precipitous fall. The patient is usually able to get up almost immediately, but may appear somewhat disoriented for several minutes thereafter.

Massive Myoclonic Type

This type of seizure varies somewhat in its clinical manifestations, but most frequently consists of a sudden flexion of the head with simultaneous extension of the upper extremities and flexion of the thighs on the abdomen accompanied by a cry. A common variation consists of a sudden generalized tonic spasm with slight trembling movements of outstretched arms that persist for several seconds or so.

The duration of a minor motor seizure (akinetic or massive myoclonic) is very brief (several seconds or so). It usually recurs frequently during the course of the day and in rapid succession (series). Many children have as many as 50 to 100 such spells daily. Minor motor seizures occur almost entirely in infants and young children who present evidence of organic brain damage (mental and physical retardation, cerebral palsies and so forth).

Gibbs, Fleming and Gibbs[2] recently designated minor motor spells as infantile spasms. These investigators reported that abnormalities, referred to as "hypsarrhythmia," were present in the electroencephalograms of 237 patients with this type of spell. The electroencephalographic abnormalities consisted of very high-voltage, random, slow waves and spikes. The electroencephalographic pattern that accompanied the clinical attack usually consisted of a discharge of fast waves and high-voltage spikes. Electroencephalograms were obtained on 386 of our patients with minor motor seizures, and abnormalities such as those reported by Gibbs, Fleming and Gibbs[2] were present in 325 (84 per cent) of the tracings.[3]

Minor motor seizures are referred to by others as petit-mal spells, petit-mal variant seizures, lightning majors, abortive grand-mal seizures, inhibitory attacks, static attacks and salaam spells. Lennox[4] includes them in his petit-mal triad.

PROPAZONE

Luton and his co-workers[1] prescribed Propazone (5-5-di-n-propyloxazolidine-2-4-dione), in dosages of 1 gm. twice daily, to a small group of epileptic patients. These workers reported that in all cases there was a reduction in number and severity of attacks. One patient was given an intravenous injection of Propazone during a convulsion. After about 5 cc. of the 10 per cent solution had been given, the patient became completely relaxed and talked to the physician. These investigators did not state what types of epileptic seizures their patients had, nor did they state the period of freedom from seizures. In 1942 Propazone was administered to 26 epileptic children,[3] with

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no favorable result in any case. Fourteen of these 26 children suffered with petit-mal epilepsy (three-per-second spike and wave dysrhythmia), and 12 had major motor epilepsy. We have searched to no avail through the literature for additional reports dealing with the use of Propazone in the treatment of epilepsy.

Tridione

Tridione (3-5-5-trimethyloxazolidine-2-4-dione) was synthesized by Spielman[5] in 1944, and its anticonvulsant properties were reported by Richards and Everett.[6] The first clinical report dealing with the use of Tridione in the treatment of epilepsy was presented by Lennox[7] in 1945. Since that time this drug has been used extensively by many investigators, who report that it is an excellent anticonvulsant for the control of petit-mal and "minor" spells.[8-25] Several workers also describe satisfactory results in the treatment of psychomotor epilepsy.[26-29] Blumberg[30] reported a good result in 1 patient with abdominal epilepsy. Most physicians agree that Tridione is of little, if any, value for the control of major motor (grand-mal) seizures.

Table 1. *Relative Effectiveness of the Various Dione Drugs in the Treatment of Petit-Mal Epilepsy (Three-per-Second Spike and Wave Dysrhythmia).*

Drug	No. of Patients*	No. Controlled†
Propazone	14	0
Tridione	804	546(68%)
Paradione	216	98(31%)
Dimedione	51	10(20%)
Malidone	19	0

*Children under 14 yr. of age.

†No recurrence of petit-mal spells during entire observation period (1 yr. or longer at time of writing).

Our results, based on the treatment of approximately 1200 children (under fourteen years of age) who suffered with the various types of epileptic seizures revealed that Tridione is primarily of value in the treatment of petit-mal epilepsy. The spells of 546 (68 per cent) of our 804 patients who suffered with petit-mal epilepsy were completely controlled by the administration of Tridione (Table 1). Only rarely were any of our patients with minor motor or psychomotor seizures favorably affected. We prescribed maximum dosages of Tridione to 181 of our patients with minor motor seizures, and in only an occasional case did we observe a satisfactory result. Gibbs, Fleming and Gibbs[2] apparently have had similar experiences with minor motor seizures.

Our findings are in general agreement with the opinion of most workers that Tridione is ineffective for the control of major motor epilepsy. It is important to note that Tridione sometimes predisposes patients to major motor seizures. Fourteen of our patients who suffered with pure petit-mal epilepsy had major motor seizures within twenty-four to forty-eight hours of the administration of the drug; Tridione also sometimes increases the frequency of pre-existing major motor seizures.[3,17,31,32]

Untoward Reactions (Table 2)

Central nervous system. Photophobia is the most frequent side reaction and occurs more often in adults than in children. Approximately 20 per cent of our patients complained of this disturbance during the course of therapy. Diplopia, vertigo, increased irritability and drowsiness were encountered, usually when excessive amounts of the drug were prescribed. Headaches, insomnia, personality changes and behavior difficulties were seen occasionally.

Table 2. *Disturbances Observed in Association with Tridione Therapy.*

Systems Involved					
Nervous	Cutaneous	Gastro-intestinal	Hemato-poietic	Genito-urinary	Cardio-vascular
Photophobia	Skin rashes	Hiccups	Leukopenia	Nephrosis	None
Diplopia	Bleeding gums	Nausea	Neutropenia Eosinophilia	Microscopical hematuria	
Vertigo	Epistaxis	Vomiting	Agranulocytosis	Granular casts	
Increased irritability	Petechial hemorrhages	Abdominal pain	Thrombocytopenia		
Drowsiness	Vaginal bleeding	Hepatitis	Pancytopenia		
Headaches					
Insomnia	Retinal hemorrhages		Hypoplastic anemia		
Personality changes	Swollen & painful joints, with fever				

Cutaneous. Skin rashes occurred in approximately 3 per cent of our patients. Morbilliform and urticarial rashes were the most frequent types observed. In 1 of our patients a hemorrhagic cutaneous reaction developed in association with a pancytopenia. Eczematoid and acneiform rashes were occasionally seen. Cutaneous reactions, consisting of an erythema multiforme of pluriorifical type and exfoliative dermatitis, have been reported.[33-35] Two of our patients had generalized swelling of the joints associated with pain and slightly elevated temperature beginning soon after the administration of Tridione; investigations for rheumatic fever were negative. In both cases the swollen joints and fever disappeared on withdrawal of Tridione and recurred when the drug was readministered. Forsey and Black[36] reported angioneurotic edema in 1 patient in association with Tridione therapy.

Gastrointestinal system. Hiccups occurred in about 4 per cent of our patients. This disturbance usually made its appearance in a week or two after the initial administration of the drug. It usually persisted for two or three days and generally disappeared spontaneously. Nausea, vomiting and abdominal pain were encountered occasionally. Leard, Greer and

Kaufman[35] reported a case of hepatitis associated with exfoliative dermatitis and abnormal bone-marrow activity occurring during Tridione therapy.

Hematopoietic system. The most serious toxic effect of Tridione is depression of bone-marrow activity; leukopenia, neutropenia, eosinophilia, agranulocytosis, thrombocytopenia, pancytopenia and hypoplastic anemia have been observed. Bleeding gums, epistaxis, petechial hemorrhages, vaginal bleeding or retinal hemorrhages are occasionally the initial presenting symptom of blood dyscrasias occurring with Tridione. Abnormal hematopoiesis usually becomes manifest at some time during the first year after the initial administration and most frequently during the first six months. We have had no deaths from hematologic disorders, but fatal cases have been reported by others.[37-45]

TABLE 3. *Dosage of Tridione.*

AGE	STARTING DOSAGE*		MAXIMUM DOSAGE*	
	METRIC	APOTHECARY	METRIC	APOTHECARY
yr.	*mg.*	*gr.*	*mg.*	*gr.*
under 6	150 (twice daily)	2½ (twice daily)	300 (3 times daily)	4⅓ (3 times daily)
over 6	300 (twice daily)	4½ (twice daily)	600 (3 times daily)	9 (3 times daily)

*Conversion of metric to apothecary system approximate.

Genitourinary system. None of our patients complained of any symptoms referable to the genitourinary system. Studies of the urine in a large number of our patients showed no abnormalities during the course of Tridione therapy. Nephrosis[46-50] has been reported, with 1 death.[50] Millichap and Kirman[51] reported microscopical hematuria and cellular casts in 8 of 12 patients treated with Tridione.

Cardiovascular system. No signs or symptoms referable to the cardiovascular system were observed in any of our patients. To our knowledge, none have been reported by others.

Dosage

The average starting and maximum daily dosages of Tridione used in treatment of our patients are given in Table 3. The optimum dosage must be determined entirely on an empirical basis, since there are no specific signs or symptoms that indicate when the maximum dosage has been surpassed.

PARADIONE

The first report dealing with the use of Paradione (3-5-dimethyl-5-ethyloxazolidine-2-4-dione) in the treatment of epilepsy was presented by Davis and Lennox[52] in 1947. Since that time the drug has been used fairly extensively but not nearly as much as Tridione.[3,17,32,36,53-55]

The results of these investigators indicate that Paradione is effective in the treatment of petit-mal epilepsy but less so than Tridione. Several physicians reported equivocal results in the treatment of psychomotor epilepsy. Paradione is essentially ineffective for the control of major motor seizures but apparently does not precipitate major motor seizures or increase the frequency of pre-existing major motor epilepsy as Tridione sometimes does.

Our findings, based on the treatment of approximately 400 children with all types of seizures, showed that this drug was effective only in the control of petit-mal epilepsy. Ninety-eight (31 per cent) of 216 of our patients with petit-mal epilepsy were completely controlled of their spells by the administration of Paradione (Table 1); none of our patients with psychomotor or minor motor seizures were affected favorably. Gibbs, Fleming and Gibbs[2] apparently have had similar results with minor motor spells.

The untoward reactions of Paradione are in general similar to those of Tridione (Table 2) but are less frequent and usually less severe. Hematologic disturbances similar to those caused by Tridione have been observed, but none of these cases, to our knowledge have been fatal.[3,17,32,52-55] Nephrosis has also been reported,[3,53,56] with 1 death.[3]

The dosage of Paradione is the same as that of Tridione (Table 3).

DIMEDIONE*

The first reports, to our knowledge, dealing with the use of Dimedione (3-ethyl-5-5-dimethyloxazolidine-2-4-dione) in the treatment of epilepsy were presented by Ellebjerg[57] and Lund[58] in 1949. In 1950 these workers, together with Saxe,[59] described a group of 123 patients with petit-mal epilepsy who were treated with Dimedione and stated that the spells were completely controlled in 31 per cent. These 123 patients were observed for periods varying from one to twelve months. No irreversible toxic reactions were encountered. These investigators reported the following disturbances: neutropenia in 11 patients, allergic skin disturbances in 10, eosinophilia in 2, nystagmus in 1 and albuminuria in another.

Fifty-one of our patients with petit-mal epilepsy were treated with Dimedione. The spells were completely controlled in 10 (20 per cent) of these patients (Table 1). No serious toxic reactions were observed in any of these patients, who received Dimedione for periods varying from two to twelve months.

MALIDONE

In 1952 Butter[60] presented a paper dealing with the use of Malidone (3-allyl-5-methyloxazolidine-2-4-dione) in the treatment of epilepsy. He stated, "25 patients with petit mal epilepsy, 15 of whom had previously been taking Tridione, were treated during the past two years with Malidone [with] therapeutic results . . . broadly similar to those obtained with Tridione, 80% of the patients deriving benefit." Butter reported no irreversible side reactions. Four per cent

*At the time of this writing Dimedione could be obtained only from Leo Pharmaceutical Products, Lovens Kemiske Fabrik, Bronskojvej 19, Copenhagen, Denmark.

of his patients had a marked leukopenia, 12 per cent manifested skin rashes and there was an increase in the occurrence of major motor seizures in 4 per cent.

Malidone* failed to control the spells in 19 of our patients with petit-mal epilepsy (Table 1); in 17 of them the attacks were subsequently controlled with Benzedrine Sulfate, Paradione or Tridione.

Discussion

Many anticonvulsant drugs used in the treatment of epilepsy fail to control petit-mal spells (transient lapses of consciousness associated with bilaterally synchronous three-per-second spike and wave forms in the electroencephalogram). Phenobarbital and Dilantin not only are not effective but also may increase the frequency of petit-mal attacks. The ketogenic diet, though exceedingly effective in minor motor or major motor epilepsy, is beneficial only occasionally in petit mal. Glutamic acid, ammonium chloride and caffeine have not proved to be of value.[3,61] We have found Benzedrine and Dexedrine sulfate to be somewhat helpful, giving complete control of petit-mal spells in 38 (11 per cent) of 344 of our patients with this form of epilepsy.

Some workers[62-64] have reported that Milontin (methylphenylsuccinimide) is of value whereas others[61,65] were unable to demonstrate any permanent control. Smith and Forster[65] reported, "Milontin appeared to have little or only a short-acting effect on the pure three per second spike and wave formations." In 1953 a group of 21 children with petit-mal epilepsy whose attacks failed to respond to Milontin but were subsequently controlled with Tridione or Paradione were reported.[3] Prenderol, which had been held to be effective in petit-mal epilepsy,[66] failed to give control in 19 children whom we treated. Likewise bromides, Mesantoin, Phenurone, Gemonil, Mysoline, Hibicon and Diamox have not proved to be effective in our experience. Atabrine (quinacrine) was reported[64,67] useful against petit-mal attacks. We have had no experiences with this drug.

The dione drugs, in our opinion, have greater effects than other drugs in the control of petit-mal spells. The relative efficiency in our hands is shown in Table 1.

The major disadvantage of Tridione, and to a lesser extent of Paradione, is its toxic effect on the hematopoietic system in some patients. For this reason we prefer to start treatment of patients with petit-mal epilepsy with either Benzedrine or Dexedrine sulfate. These drugs are effective in some patients with petit-mal epilepsy, but they are by no means as effective as either Tridione or Paradione. However, since both Benzedrine and Dexedrine sulfate are essentially innocuous drugs, we believe that it is advisable to give either a trial before Paradione or Tridione is prescribed.

Since one cannot predict in which patient the hematopoietic system is likely to be affected adversely by the administration of either Tridione or Paradione, complete blood counts should be made on all patients receiving these drugs before the institution of therapy and at monthly intervals thereafter. If no abnormalities occur within twelve months the interval between counts may be extended. The parents, or the patient, should be instructed to report immediately any sign or symptom of possible damage to the hematopoietic system, such as fever, sore throat, easy bruising, petechiae, ecchymosis, epistaxis or vaginal bleeding. When there is a significant reduction in the white-cell or red-cell count or platelets the drug should be withdrawn immediately. For example, it is our policy to discontinue the use of the drug in patients in whom the total white-cell count drops below 3500 or in whom there is a marked percentage reduction in the neutrophils. The drug may be readministered when the blood count returns to normal. In such cases, however, check-up blood counts should be made twice a week for a month or so.

In view of the occurrence of nephrosis in association with Paradione and Tridione therapy, the urine of all patients receiving these drugs should be examined every two weeks. The other untoward reactions of Paradione and Tridione have not proved to be too disturbing. The drug should be withdrawn immediately when rashes appear. It may be prescribed again for those patients with the milder cutaneous reactions, but only after the rash has disappeared completely. Photophobia apparently has no lasting ill effects, but may cause much discomfort in those severely affected. Dark glasses minimize the discomfort in some cases. Sloan and Gilger[68] made serial ophthalmologic examinations on a group of patients treated with Tridione and observed temporary impairment of visual acuity, sensitivity to brightness, color discrimination and sensitivity to flicker in each case. In patients studied for more than three months tolerance to these visual effects developed. Sloan and Gilger believe that these phenomena suggest that the neutral layers of the retina rather than photochemical processes are involved. So far as is known, no permanent anatomic changes are produced.

Summary and Conclusions

The results of the use of five dione drugs (Propazone, Tridione, Paradione, Dimedione and Malidone) in the treatment of the epilepsies are reported. Tridione is the most effective drug for the control of petit-mal epilepsy (three-per-second spike and wave dysrhythmia), these spells being completely controlled in 546 (68 per cent) of 804 patients. It is essentially ineffective against minor motor and major motor seizures. Several workers have reported good results in the treatment of a few patients with psychomotor epilepsy.

We believe that the risk of irreversible hematologic damage, the major objection to Tridione and, to a

*Kindly supplied by Wynlit Pharmaceuticals, Incorporated, Philadelphia.

lesser extent, Paradione, is not very great if patients receiving Tridione are adequately supervised with periodic physical examinations and complete blood counts. We have treated approximately 1200 children with Tridione. To date, no fatal reactions have developed in patients directly under our care.

Paradione, the second most effective drug for the treatment of petit-mal epilepsy, also is sometimes toxic to the hematopoietic system. Therefore, the same precautionary measures recommended for Tridione therapy should be employed for Paradione therapy.

Dimedione may be an effective drug for the treatment of petit-mal epilepsy. The difficulty in obtaining this drug makes its use considerably limited in this country. We believe that further study in a larger group of patients over a more extended period is necessary to substantiate its value. Propazone was not effective in our hands, and it appears that this drug is no longer in use. Our experience with Malidone was very disappointing.

Our results, and also those of some others, with other drugs (glutamic acid, Milontin, Diamox and so forth) recommended for the treatment of petit-mal epilepsy have not been good. The diversity of these results may be explained by the fact that the term "petit mal" is used by many investigators to include many types of epileptic spells, including minor motor seizures. It appears that many physicians designate as petit mal all spells of short duration, regardless of the electroencephalographic patterns. We reserve the term "petit mal" for spells that consist of transient lapses of consciousness associated with bilateral synchronous three-per-second spike and wave forms in the electroencephalogram.

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MEDICAL INTELLIGENCE

PUERPERAL FAT EMBOLISM*

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FAT embolism is usually related to the effects of trauma on the skeleton; it has also complicated surgery involving adipose tissues. Recently, a case was observed in the early puerperium. With the exception of Warthin's[1] case, similar occurrences have not been described in medical publications. The rarity of this puerperal complication prompts its report.

CASE REPORT

A 39-year-old Negress, a gravida ii, was admitted to the Bridgeport Hospital on November 13, 1954, at 2:20 p.m., in the 40th week of pregnancy in early labor. She had been hospitalized 2 years previously for a normal, full-term spontaneous delivery of a living infant. The current pregnancy was accompanied by hypertension, occasional albuminuria, 30-pound weight gain and edema of the lower extremities. Labor pains began about 2 hours before admission and were well established by 4:30 p.m. Physical examination disclosed a short, obese woman in active labor. The temperature was 99°F., the pulse 88, and the respirations 20; the blood pressure was 210/100. Slight periorbital puffiness was present. The retinas were not examined. The heart and lungs appeared to be unremarkable. The uterine fundus was felt beneath the xiphoid cartilage. Fetal heart sounds were heard at a rate of 144 in the left lower quadrant. The labia majora were moderately edematous.

Urinalysis was not performed. The hemoglobin was 12.7 gm. per 100 cc., and the hematocrit was 40 per cent.

The fetal membranes were ruptured operatively at 7:45 p.m. The slow course of labor was attributed to a posterior occipital presentation, and the fetal head was rotated manually by a consultant and low-forceps extraction of a stillborn infant was accomplished at 8:55 p.m. under closed nitrous oxide, oxygen and ether anesthesia. The placenta delivered spontaneously 5 minutes later. Repair of the episiotomy incision was unusually difficult because of numerous, large varices distributed circumferentially about the vaginal introitus. An estimated blood loss of 750 cc. was replaced by transfusion. During the perineal repair, at about 9:30 p.m., the respirations ceased, the skin was noted to be cool and moist, and the pulse was imperceptible. Norepinephrine, as well as 500 cc. of whole blood, was infused and the blood pressure was found to be 40/0. Shallow respirations returned at 9:45. The patient reacted to painful stimuli; corneal reflexes returned, and the blood pressure rose to 110/60. At 11:30 p.m. respirations ceased again, the blood pressure was unobtainable, and cardiac massage was begun together with intracardiac injection of epinephrine. These measures failed to resuscitate the patient, who was pronounced dead at 12:30 a.m., approximately 3½ hours after delivery. The clinical diagnosis was pulmonary embolism due to amniotic-fluid particles.

At post-mortem examination significant gross findings were observed. The right lung was expanded, and the left collapsed, and weighed 260 and 190 gm. respectively; there was no gross evidence of pulmonary edema. The tracheobronchial tree was unremarkable, and the pulmonary vessels were free of emboli. The heart weighed 400 gm., and the left ventricular wall was 19 mm. in thickness; the coronary-artery system appeared to be within normal limits, with no gross suggestion of recent or remote cardiac infarction. The liver weighed 1700 gm. and appeared grossly normal. The spleen, which weighed 230 gm., was normal in shape and consistence. Each kidney weighed 230 gm., and on cut sections the cortexes were very pallid in contrast to the congested medullas. The uterus was boggy and extended to the umbilicus; the periuterine veins were patent. The brain weighed 1130 gm. and on external examination appeared to be normal.

On microscopical examination, in the hematoxylin and eosin preparations, numerous sections of the lungs, brain and kidneys presented many arterioles and capillaries that were dilated but devoid of blood cells. Fat-stained preparations demonstrated that the dilated arterioles and capillaries were filled with sudanophilic droplets that could be seen to be taking the shape of the vascular lumens, often branching into subsidiary channels. The fat droplets were found in nearly every low-power field in the lung sections and in about 1 of 5 low-power fields in the brain. No associated inflammatory or degenerative changes were found. The lungs were carefully examined for amniotic-fluid constituents, but none were found. The final anatomic diagnosis was multiple fat emboli involving the lungs and brain.

DISCUSSION

Gauss[2] defined fat embolism as "an acute circulatory disturbance caused by trauma, manifested anatomically by the presence of fat globules within the vessels of the circulation and by certain secondary changes which these produce; clinically it is recognized by the presence of restlessness, dyspnea, delirium, coma and, frequently death." The pathophysiologic mechanism involves injury to adipose tissue, resulting in the liberation of intracellular fat; disrupted and patent venous radicles; and the development of local pressure gradients directing the passage of free fat into the open veins. Although it is likely that in most cases of trauma the first two factors obtain, fat embolism does not result because of the absence of the third factor. The propensity for fat embolism to occur with greatest frequency after trauma to bone may be attributed to the presence of venous radicles within calcified tubules that prevent their collapse. A mechanism for fat embolism occurring after soft-tissue injuries is not as readily demonstrable. In the case reported above, the presence of numerous fat emboli in the lungs and brain and to a lesser extent in the kidneys and the absence of other pathologic changes appear to justify the diagnosis of fat embolism. It is postulated that trauma associated with obstetric manipulation and passage of the fetal parts in an extremely obese patient liberated enough

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fat and provided adequate regional pressure changes to force free fat into the numerous pudendal and perineal varices.

Gross and microscopical evidence of fat embolism may vary considerably, depending on the interval between the time of trauma and death. Thus, Warren[3] observed in cases of rapid death nothing grossly beyond an excess of oily droplets in the pulmonary circulation. When the interval between trauma and death was many hours pulmonary edema and perivascular petechiae were found in the brain. Microscopical preparations demonstrated fat droplets in the small vessels and capillaries of most tissues; these were found predominantly in the lungs and glomeruli and varied in size from a few microns to 1 cm. or more. Gauss was impressed with the fact that the greatest anatomic disturbance in fat embolism occurred in the central nervous system; he found microscopical evidence in sections of the spinal cord, spinal-root nerves, cerebellum, basal nuclei, corpus callosum and cerebral cortex.

Both the duration and the character of the syndrome associated with fat embolism are variable. Thus, Burger is cited by Warren as having suggested the delineation of three forms of fat embolism: peracute, with death in a few seconds; acute, with symptoms immediately after injury and death in hours to days; and subacute, with a free period between the time of trauma and the appearance of symptoms. Characteristically, the syndrome includes pulmonary and cerebral components: increased respiratory rate, dyspnea, pallor, cyanosis, expectoration of bloody, frothy sputum, confusion, restlessness and convulsions terminating in stupor or coma.

The possibility of diagnosis during life was investigated by Musselman et al.[4] on the basis of the finding of fat in the sputum and urine. Their conclusion was that the demonstration of free fat in the urine was a practical confirmatory test for fat embolism although some patients might be falsely included or excluded. Their frequent finding of fat in the sputum in the absence of fat embolism indicated its unreliability as a diagnostic aid.

Fat embolism in the puerperium has rarely been observed. Virchow is cited by Groskloss[5] as having reported a case of fat embolism due to injury imposed on the pelvic fatty tissue by passage of the fetal head through the birth canal. Warthin[1] included in his study a case of fat embolism in an eighteen-year-old eclamptic patient who died three days after the delivery of twins; in this case fat emboli were found only in the lungs. Denman and Gragg[6] observed "scarce" fat emboli in a patient who died of toxemia of pregnancy.

In the puerperium embolism is frequently associated with pelvic or crurofemoral thrombophlebitis. Amniotic fluid as a source of emboli in the puerperium was first described by Steiner and Lushbaugh.[7] Air embolism occurring during term labor was discussed by Waldrop,[8] who also reviewed 17 previously reported cases of puerperal air embolism. To these established causes of embolism in the puerperium multiple fat embolism should be added.

Summary

A case of sudden, unexpected death in the early puerperium associated with the finding of multiple fat embolism is presented. It is suggested that the trauma of childbirth was the exciting factor.

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BY THE LONDON POST

The Royal Society of Medicine—The Ban on Heroin

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LONDON, ENGLAND

IN the year 1773 the Medical Society of London was created so that physicians might exchange views and compare their observations with those of others. Many similar societies were formed at about the same time, and although the Medical Society of London still flourishes as one of the most honorable of the profession, it is because of a few stormy passages in its early days that the Royal Society of Medicine can trace its origin to the year 1805.

It seems that the influence of a certain Dr. James Sims began to dominate the activities of the Medical Society of London soon after its formation, and in 1786 he was made president, remaining in the presidential chair for twenty-two years. He became autocratic, and eventually, in 1805, an effort was made to limit the tenure of the president's office to three years. This resolution was rejected at a general meeting, but 26 of the members of the Society were so disgruntled that they decided to secede from it and formed a new society, meeting at the Freemason's Tavern in London on May 22, 1805. They resolved "that a society comprehending the several branches of the medical profession be established in London for the purpose of conversation on professional subjects, for the reception of communications and for the foundation of a library." They named the society the Medical and Chirurgical Society of London, the Royal Charter being granted in 1834 after a certain display of jealousy by the Royal College of Physicians.

During the latter part of the nineteenth century, various specialist societies sprang up, and when the council of the Royal Medical and Chirurgical Society

met on May 22, 1905, to admit the Prince of Wales as an honorary fellow and to celebrate its centenary, plans for an amalgamation of these societies and for the formation of the Royal Society of Medicine were made. This society now has nearly 10,000 fellows, with 26 sections holding more than 200 meetings each year. The Library, founded by the original 26 members in 1805, contains about 250,000 books and journals. The new library accommodation recently opened was made possible by a generous gift from the Wellcome Trust.

The hundred and fiftieth anniversary of the date of origin of the Royal Society of Medicine was marked by the publication of a commemorative volume on the history of the Society, written by Dr. Maurice Davidson, and by a banquet at which the Duke of Edinburgh was present and at which honorary fellowship was conferred upon him. In conferring this privilege, Sir William Gilliatt, the president, recalled that the Society had long been favored with royal patronage and that King William IV was the first royal patron. He assured the Duke that the fellowship had been offered to him in recognition of his distinguished services to science and that with other fellows he would now have the right to borrow 8 books at any one time from the library. He was sure that almost any mood could be satisfied from the vast range of literature available.

After handing the Duke his certificate of fellowship Sir William asked Dr. Maurice Davidson to present him with a copy of his commemorative volume. The Duke graciously acknowledged his election and expressed his thanks for the book (though he mentioned that he hoped he would be forgiven for saying that he had rather hoped there might have been a gold-plated stethoscope for him!).

He congratulated the society on its hundred and fiftieth birthday and recalled the state of medical knowledge at the time of its origin. He urged people who often wished that they lived in another age to remember that there were no anesthetics and no antiseptics at that time. After all, about that time, there was as much excitement about Robert Liston's thirty-second amputation of the leg as there is today about Roger Bannister's four-minute mile. The Duke understood that Bannister had run through three trainers, but Liston ran through an assistant's three fingers! The Duke was sure that he preferred to live in this day of rapidly advancing science even if one had to reckon with the hazards of strikes and atomic energy. Speaking on a more serious note, he stressed as a layman how important he believed it to be that the doctor-patient relation should remain a personal one. In this respect he graciously acknowledged the help that Sir William Gilliatt (the royal obstetrician) had given to his own family, and explained that it was for this reason above all others that he was glad to have received the fellowship of the Society from his hand and to be sitting at his side that evening.

Sir Arthur Porritt proposed the toast of the guests, and replies were made to this toast by the Marquess of Salisbury, K.G., and Lord Adrian, O.M., F.R.S. The latter, who was present as a guest in his capacity as president of the Royal Society, explained that he had been a fellow of the Royal Society of Medicine for more than thirty years and that he felt something of an impostor when asked to attend the banquet as a guest. Speaking of the present-day value of the Society he pointed out that, in the modern welfare state, the physicians and surgeons must necessarily have great obligations to the state, which finances the Health Service and provides amenities for the people. He thought the value of the Royal Society of Medicine was that its fellows comprised all sorts of doctors who could forget their obligations to the state at No. 1 Wimpole Street. If the Society went out of business he believed that medicine would lose a vital organ, for it was the acknowledged meeting place for experts to discuss their findings. He hoped it would forever remain an independent body because he considered independence the greatest promoter of medical science.

* * * *

In accordance with the recommendation of the Economic and Social Council of the United Nations, the British Government has banned the manufacture of heroin in this country after the end of the year, either for export or for domestic use. This decision has caused a wave of righteous indignation to arise from the medical profession, perhaps chiefly on the grounds that its members were not fully consulted before the decision was taken.

It has been argued that there are certain cases, particularly of advanced carcinoma, in which heroin is the most efficient pain reliever, with no satisfactory substitute available. It is appreciated that heroin addiction is a major problem in many countries, but in Great Britain there are only about 40 known heroin addicts. The *Times* asks, therefore, whether it would not have been sufficient if the export of the drug had been banned.

The medical profession claims that none of the new synthetic substitutes are as efficient a pain reliever as heroin, and that, according to latest figures, there are now almost as many addicts to pethidine in this country as there are to heroin. On the other hand it cannot be denied that by placing a ban on heroin the British Government is doing no more than stepping into line with the great majority of United Nations members, many of which have also had no serious trouble with addiction to the drug.

Nevertheless, a motion seeking the reversal of the Government's decision was carried at the recent annual representative meeting of the British Medical Association, stating that heroin is of inestimable value. The motion recommended that it should still be manufactured in this country for medical use, but that its export should be banned. The Council was instructed to seek direct access to the Government, but the present indications are that the Government will stand by its decision to impose the ban.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41301

PRESENTATION OF CASE

A fifty-two-year-old woman was admitted to the hospital because of low-back pain.

One month previously, after twisting her back, the patient had a dull, aching pain in the lumbosacral area that persisted, increased in intensity and did not respond to hot packs and aspirin. She was admitted to another hospital ten days later, when she developed a persistent lower abdominal pain that spread across the low back, extended up to the iliac crest and increased on motion. It was not alleviated by hot packs, aspirin or intramuscular injection of Demerol. She was referred to this hospital for further evaluation.

At the age of fourteen the patient fractured the left knee and was hospitalized for a period of eighteen weeks. She was told that she had "rheumatic fever," but the pain in the hands and feet was poorly described. She was admitted to this hospital eleven years before admission after she had had stiffness, pain and swelling in the fingers and arms for four years and fatigue and low-back pain for two years. Physical examination at this time revealed swelling of the fingers of both hands, with small nodules in the distal interphalangeal joints. There was slight limitation of dorsal flexion in the left ankle and limitation of motion in the lumbar spine, without pain on motion. The hemoglobin was 13.4 gm. per 100 cc., with a normal differential and white-cell count. The uric acid was 4.3 mg., the calcium 9 mg., the phosphorus 3.9 mg., and the alkaline phosphatase 1.5 units per 100 cc. X-ray films of the lumbar spine and pelvis were not remarkable. There were cystic punched-out areas in adjacent bones of the proximal middle phalanges of both second fingers and the middle phalanx of the fifth finger of the right hand. After this hospitalization she had intermittent and sporadic attacks of pain, which became worse on motion of the hands, feet and low back. These attacks although severe were not disabling, and she continued to work until one month before admission.

Physical examination showed an apprehensive, moderately pale, well nourished woman complaining of back pain. There was an ill defined area of tenderness of the sacrum on palpation and limitation of flexion of all digits, with marked weakness of the hands and minimal wasting of the small muscles of the digits. Heberden's nodes were present on all digits. Several inguinal lymph nodes were palpable. The spleen was felt 3 or 4 fingerbreadths below the left costal margin, and the liver was palpable about 4 fingerbreadths below the right costal margin. The heart was not enlarged, and no murmurs were heard. Rectal and pelvic examinations were not contributory.

The temperature was 98.6°F., the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 10.5 gm. per 100 cc. and a white-cell count of 8200, with 92 per cent neutrophils, 5 per cent eosinophils and 2 per cent monocytes. The platelets were normal or slightly increased. The red cells were normocytic, slightly hypochromic and slightly basophilic, with slight to moderate anisocytosis and poikilocytosis. No immature or plasma cells were seen. The sedimentation rate was 48 mm. in one hour. The fasting blood sugar was 100 mg., the nonprotein nitrogen 32 mg., the total protein 6.0 gm., the calcium 8.8 mg., the phosphorus 3.2 mg., the alkaline phosphatase 6.0 units, and the uric acid 3.2 mg. per 100 cc. The serum electrophoretic pattern was normal. The blood Hinton test was negative. Stool guaiac tests were negative on three occasions. X-ray films of the lumbosacral spine showed a minimal narrowing between the fifth lumbar and first sacral vertebras; other than this the bones were not unusual (Fig. 1). The spleen was enlarged. An intravenous pyelogram revealed the kidneys to be normal in size, shape and position, but the left renal collecting system was not well outlined.

FIGURE 1. *Anteroposterior Abdominal Film, Showing the Greatly Enlarged Spleen, Which Displaces the Kidney Medially.*

Contrast substance is visible in both urinary passages.

The patient remained fairly comfortable at rest on

aspirin and codeine but had severe pain when moved. A bone-marrow examination on the sixth hospital day (right iliac crest) revealed very cellular material. Megakaryocytes were moderately increased; there were 30 per cent erythroid cells, 63 per cent myeloid cells, 4 per cent reticulum cells, 1 per cent plasma cells and 2 per cent blasts. A smear showed the red cells to be generally normocytic, slightly hypochromic and slightly basophilic, with moderate anisocytosis. The alkaline phosphatase rose to 8.0 units per 100 cc. On the eighth hospital day the hemoglobin dropped to 6.6 gm. per 100 cc. The serum bilirubin was 1.5 mg. per 100 cc., rising to 8.2 mg. preoperatively; the prothrombin time varied from 38 to 60 per cent, and the reticulocyte count was 12.0 per cent, the Coombs test was negative and the urinary bilirubin was negative. Stool guaiac tests were negative. The patient was transfused and started on cortisone. Despite transfusions of 4000 cc. of whole blood over a period of ten days the hemoglobin continued around levels of 6 to 8 gm. per 100 cc. ACTH was added to the therapeutic regimen. The patient became jaundiced, and the urine gave a + test for bile and was guaiac negative. During the day before operation she became dyspneic; the pulmonic second sound became greater than the aortic; the lungs showed dullness to flatness at the left base, with diminished breath sounds and egophony. She was digitalized and given Mercuhydrin. An x-ray film of the chest demonstrated cardiac enlargement and fluid in the left pleural cavity (Fig. 2).

The patient's blood type was O-Rh positive. The direct Coombs test was repeatedly negative, and the indirect Coombs test was initially weakly positive with some of the cells and later positive with most of the "O" cells tested. The cold-agglutinin titer was 1:32. The patient's serum showed strong agglutination, both at room temperature and at body temperature, of every sample of "O" blood tested. An operation was performed on the twenty-third hospital day.

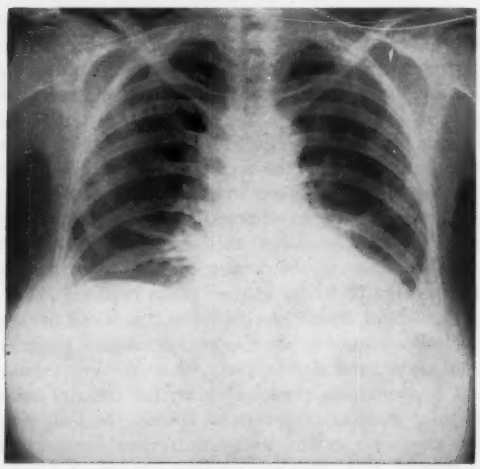

FIGURE 2. *Posteroanterior Film of the Chest, Showing Enlarged Right Paratracheal Lymph Nodes (Arrows). The left ventricle is prominent. A small amount of fluid is present at the left base, and there are atelectatic streaks in both lower lungs.*

DIFFERENTIAL DIAGNOSIS

DR. MARIO STEFANINI*: This history provides so many clinical data that it is difficult to fit them into a proper order. It seems to me that there are four significant findings in this case: hepatosplenomegaly and lymphadenopathy; hemolytic anemia as a complicating feature; the presence of bone disease that, from the description of its radiologic appearance and from the serum alkaline phosphatase level, seems to have been osteoblastic in nature; and the terminal rise in direct-reacting serum bilirubin (+ test for bile in the urine). Before I discuss the differential diagnoses I should like to see the x-ray films.

DR. BERNARD M. JACOBSON: It was inadvertently omitted in the protocol that one x-ray film of the chest taken in another hospital before admission was said to be normal.

DR. JOSEPH HANELIN: I should question that; I have one film of the chest that shows definite abnormality.

X-ray films of the hands made nine years before admission show peculiar changes in a number of the proximal interphalangeal joints, many of which are narrowed. The articular cortex is partially destroyed, and large cystic zones are seen in the heads of the proximal phalanges of both index fingers. There is also narrowing of the distal interphalangeal joints. The bones of the hands are well calcified. The films of the lumbar spine taken at that time are normal, as are the films on admission. The abdominal film demonstrates the large spleen (Fig. 1). The kidneys themselves are normal in size and shape although the left kidney is displaced slightly medially, probably by the large spleen. Both kidneys are functioning well. The protocol is misleading in suggesting that there was some abnormality on the left side. I think that visualization is not ideal rather than that any abnormality is present. The posteroanterior film of the chest shows a prominence in the right paravertebral region suggesting adenopathy (Fig. 2). The heart is slightly enlarged; there is some fluid at the left base, and atelectatic streaks are scattered in the lungs.

DR. STEFANINI: The first diagnosis that I should like to consider and to eliminate is lupus erythematosus disseminatus. This diagnosis should always be kept in mind when hemolytic anemia develops in a patient who has arthritic symptoms, a large spleen and a large liver. However, the marked lymphadenopathy, the absence of leukopenia and the bone-marrow picture are not in agreement with it.

The second possibility that I shall discuss briefly is sarcoidosis. This disease could have produced the punched-out areas that were described in the distal

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phalanges of the patient's hands; it may, moreover, be complicated by hemolytic anemia and cause an osteoblastic type of bone disease, adenopathy and hepatosplenomegaly. In this patient, however, pulmonary lesions were not typical of sarcoidosis; moreover, when sarcoidosis is extensive and produces disseminated lesions, it also involves more and differently located lymph nodes than were affected in this patient (commonly, the cervical and axillary lymph nodes and lachrymal and salivary glands). Also, although it may rarely be normal, the serum protein electrophoretic pattern is usually abnormal through the increase in beta and alpha globulin fractions. Sarcoidosis, therefore, seems to be a remote possibility in this patient.

Multiple myeloma should be discussed as another possibility since this entity seems to be able to simulate so many diseases. Hepatomegaly is consistent with the disease. Other findings, however, are strikingly against it. Significant splenomegaly, lymphadenopathy and hemolytic anemia are only very rarely features of multiple myeloma. The normal serum protein electrophoretic pattern and the lack of renal involvement (urinalysis was negative for albumin and serum nonprotein nitrogen and uric acid were normal) also make such a diagnosis unlikely.

Lymphoma is, in my opinion, the most probable diagnosis in this case. This conclusion can be based on a number of pertinent facts: the rapidly progressive course of the disease and the presence of lymphadenopathy, hilar adenopathy, splenomegaly and hepatomegaly. Osteoblastic lesions, however, are exceptional, although they may be seen in Hodgkin's sarcoma. Biopsy of a lymph node and aspiration of splenic or lymph-node material would have been of value, I believe, in establishing the diagnosis of the type of lymphoma. The characteristics of the bone marrow, showing lack of lymphoblastic infiltration but, rather, a moderate increase in the percentage of reticulum cells and of megakaryocytes and, generally, hypercellularity, seem to favor the diagnosis of lymphoma, Hodgkin's type.

With a tentative diagnosis in mind, a few points remain to be discussed. One is the association of acquired hemolytic anemia with lymphoma. Several mechanisms may cause increased red-cell destruction in this disease. One is sequestration and lysis of red cells in an enlarged and, presumably, hyperactive spleen; the other is erythrophagocytosis taking place in the spleen as well as in other organs; the third is intravascular agglutination and lysis of red cells by autoimmune antibodies. In the last, the spleen may co-operate by destroying cells agglutinated or damaged by the antibody. In this patient, as in most, more than one mechanism of red-cell destruction was likely at play. Two were easily demonstrable since the spleen was considerably enlarged and, at the same time, there was evidence of free red-cell antibodies in the patient's serum. We are told that the serum agglutinated cells at room temperature and at body temperature, irrespective of blood group and type. Presumably, autoimmune red-cell antibodies were also present.

It is of interest to speculate on the mechanism of production of red-cell antibodies in patients with lymphoma. In chronic lymphocytic leukemia, while it is fairly common to observe autoimmune hemolytic anemia, it is generally held that lymphocytes and lymphoblasts either produce the antibody directly or represent the antigenic stimulus for its formation, perhaps because lymphocytes and red cells can have common antigens. The formation of antibodies in Hodgkin's disease and other lymphomas is more rare and obscure, but could take place through a similar mechanism. In any event acquired hemolytic anemia is a serious complication that creates many therapeutic problems. I am sure that ACTH and cortisone were used in adequate doses; it is of interest that the physicians failed to control the hemolytic process in this patient. That failure perhaps suggests the predominant role of splenic mechanisms of erythrophagocytosis and red-cell lysis.

Another problem concerns the presence of a strong red-cell cold-agglutinin titer. It is important that this phenomenon be distinguished from red-cell rouleau formation, and I wonder if it was kept in mind in the interpretation of the findings. Because of the high titer I am sure that this was true agglutination. This phenomenon and others of immunologic nature found in leukemia and lymphoma (like a + heterophil test due to a Forssman antibody) are not uncommon, perhaps because of the significant changes in plasma protein distribution found in these diseases. From this viewpoint, the normality of the patient's electrophoretic serum protein pattern poses an interesting question that I am unable to answer.

A third problem is the progressive increase of alkaline phosphatase and of the direct-reacting bilirubin in the terminal phase of the disease. Although the first finding suggests progressive invasion of the bone by the disease, the accompanying rise in direct-reacting bilirubin, shown by the appearance of bile in the urine, clearly suggests biliary obstruction and raises the question whether these findings could not have been due to obstruction of the biliary tract by enlarged lymph nodes at the "porta hepatis."

The final picture of this patient before operation had other features, like the uncontrollable hemolytic anemia and the development of severe heart failure and hydrothorax, presumably on the basis of severe anemia. Splenectomy was, of course, the only resort in a case such as this, in which medical means failed to control the hemolytic process. I am inclined to believe that surgery revealed, in addition to the enlargement of abdominal and retroperitoneal lymph nodes, the enlarged, congested spleen we know to be typical of hemolytic anemia.

DR. WINFIELD S. MORGAN: Dr. Short, have you a comment?

DR. CHARLES L. SHORT: I saw this patient eleven years before admission for arthritis, chiefly of the hands. At that time the diagnosis of degenerative

joint disease with especial involvement of the proximal phalangeal joints was made. She also had Heberden's nodes in the terminal phalangeal joints and an unusual x-ray picture showing cyst formation. Cyst formation is found commonly in degenerative joint disease adjacent to the hip joints but not as commonly in relation to the finger joints. The picture was thought not to be that of sarcoidosis or of rheumatoid arthritis, but an unusual type of degenerative joint disease. When I saw her on this admission it was also for study of arthritis. It was thought that the back pain might be caused by arthritis. Again, she did not have signs of rheumatoid arthritis, and the fingers had changed little over the years. It was thus not possible to explain the increased sedimentation rate, the anemia and the splenomegaly on the basis of rheumatoid arthritis. From that time on, our reasoning was similar to Dr. Stefanini's. This patient demonstrated the old adage: if narcotics are necessary to relieve pain that is ascribed to arthritis, the patient probably has a more serious lesion, usually neoplastic.

DR. JACOB C. LERMAN: I am intrigued by the punched-out areas of bones. I was trying to recollect whether or not lymphoma can produce those lesions and last this long. Myeloma can and may be present for a long time. Moreover, the total protein, albumin-globulin ratio and electrophoretic pattern of serum protein may be normal.

DR. SHORT: Those punched-out areas were there eleven years before. I think that one cannot connect them with the disease responsible for her death.

DR. JACOBSON: As the alkaline phosphatase rose, the jaundice clinically seemed to increase. Later, bile appeared in the urine. We believed that in addition to hemolytic jaundice she had obstructive jaundice and that probably the marked elevation of the alkaline phosphatase was due not to bone disease but to obstructive jaundice. That impression was also confirmed by the direct bilirubin of about 3 mg. and the total bilirubin of 3.5 mg. per 100 cc.

I appreciate Dr. Stefanini's careful analysis of the diagnostic possibilities in this case. I wonder why he left out, as the evidence against myeloma, the normal bone marrow.

DR. STEFANINI: The reason for this deliberate omission is that recently I have seen a small series of solitary myelomas (myelomas within the bone in patients who had no bone-marrow or blood manifestations). Thus, one patient presented three punched-out areas — one in the right humerus, one in the skull and one in a rib — that were diagnosed as multiple myeloma by needle biopsy. This patient had no evidence of myeloma in the bone marrow or peripheral blood. Thus, negativity of the bone marrow cannot be considered absolute evidence against a diagnosis of multiple myeloma.

DR. MORTEN GROVE-RASMUSSEN: This patient presented a few problems from the serologic angle, and, as Dr. Stefanini said, we had to be sure that this was not rouleau formation but a real agglutination. I think the titer of 1:32 rules out the possibility of rouleau formation, with which the titer is not usually so high. The antibodies were nonspecific; they were tested in saline solution and serum albumin medium and with trypsinized cells. On the other hand the indirect Coombs test showed specificity in the beginning so we really thought we were dealing with an anti-E antibody, and, of course, these specific Rh antibodies have been described several times in cases of acquired hemolytic anemia. Later, the indirect Coombs test became positive with all our cells. We tested up to 14 cells in all, and it was impossible to detect any specificity. The negative direct Coombs test can probably be explained on the basis of the fact that the coated red cells are so quickly eliminated that we do not have a chance to pick them up.

DR. MORGAN: Dr. Donaldson, we will call on you for the surgical description.

DR. GORDON A. DONALDSON: We were called in as mechanics in this case although the diagnosis was clouded in the minds of the physicians. We scheduled the patient for a splenectomy as an emergency procedure. We approached the spleen directly. It was free and large, three or four times the normal size, and was delivered. In addition to the main spleen two accessory small spleens were found. (Actually, the surgeon should look for additional spleens in any patient with hemolytic anemia.) We discovered a small retroperitoneal mass and on further exploration found other masses. One in particular in the region of the caudate lobe of the liver was quite large, 12 cm. by 4 cm., and was cystic in one area. That mass compressed the common duct and seemed to arise from behind the pancreas.

CLINICAL DIAGNOSES

Hemolytic anemia.
Lymphoblastoma.

DR. MARIO STEFANINI'S DIAGNOSES

Lymphoma (?Hodgkin's disease), with osteoblastic involvement of bone.
Acquired hemolytic anemia.
Obstructive jaundice.
Heart failure.

ANATOMICAL DIAGNOSES

Malignant lymphoma, lymphoblastic type, involving spleen, bone marrow, lymph nodes and liver.
(Acquired hemolytic anemia.)

PATHOLOGICAL DISCUSSION

DR. MORGAN: The spleen was much enlarged, weighing 700 gm., and had a smooth, tense, shiny capsule. The cut surface showed gray-white foci against a purplish-red background having the distribution of malpighian corpuscles but measuring several times larger than the malpighian corpuscles seen normally. Microscopically, this enlargement proved to be the result of infiltration of these areas by

malignant lymphoma of the lymphoblastic type, the tumor cells being fairly uniform in shape and size but somewhat less mature than lymphocytes. In addition, the sections revealed marked congestion as manifested by the presence of large lakes of blood. On re-examination of the bone-marrow aspiration from the iliac crest taken earlier lymphoblastic foci similar to those in the spleen were seen. These had been noted at the time of the original examination, but since one may see lymphoid follicles normally in bone marrow, we did not consider the findings sufficient to warrant a diagnosis of malignant lymphoma.

Postoperatively, this patient was given repeated transfusions and did fairly well for the first two days except that jaundice increased somewhat. On the third day she developed generalized purpura and died. At autopsy the right pleural cavity contained 600 cc. of serous fluid, and the left 1200 cc.; the peritoneal cavity contained 750 cc. of similar fluid. There was generalized lymphadenopathy, and this was particularly marked in the retroperitoneal region, where there were lymph nodes measuring up to 6 cm. in greatest dimension. The common bile duct was not considered to be compressed or dilated although this would not necessarily mean that it was not compromised to some degree during life. Although the liver was within normal limits, weighing 1400 gm., microscopical examination disclosed considerable lymphomatous infiltration, usually confined to the portal regions. There was also a moderate degree of bile stasis; this may have been due to extrahepatic pressure on the biliary tree by lymph nodes, but it may also have been due to intrahepatic pressure on the biliary radicles by the tumor infiltration in the portal areas. Sections of the spine revealed aggregations of cells of a lymphoblastic type scattered throughout marrow of essentially normal quantity and composition. At least in the sections we had for study there were no osteoblastic lesions, and the encroachment or replacement of marrow by tumor was not very striking.

DR. JACOBSON: In answer to Dr. Stefanini's question about biopsy before operation, none of us believed that the lymph nodes were worth biopsying. We hesitated to do a liver or spleen puncture because the prothrombin time was so prolonged in spite of fresh blood transfusions and massive doses of vitamin K.

DR. STEFANINI: This explains to me the reason for the special attention given to the prothrombin time. I should like to say at this point that in my experience the plasma prothrombin time has limited importance in the selection of cases for liver or splenic biopsies. We have found that severe thrombocytopenia and a prolonged bleeding time are much more important contraindications to biopsy procedures than a prolonged plasma prothrombin time. In fact we have done biopsies in the presence of plasma prothrombin activity as low as 20 per cent without complications, when platelet count and bleeding time were within normal limits.

CASE 41302

PRESENTATION OF CASE

A fifty-nine-year-old woman entered the hospital because of massive bleeding by rectum.

Six weeks before entry the patient began to pass bulky, black stools. For a month previously she had been taking a polyvitamin preparation including iron (1 pill per day). With the onset of the tarry stools she became slightly constipated and began to experience dyspnea and profuse sweating on exertion. Four days before admission she consulted a physician, who noted her pallor and found her hemoglobin to be low. On the morning of admission she noted marked borborygmus over the entire abdomen. Two hours later she passed several copious, wine-red, liquid stools.

There was no history of abdominal discomfort, nausea, vomiting, diarrhea, food intolerance or jaundice. The patient stated that she tended to bruise easily but had had no significant bleeding in the past. Intake of alcoholic beverages was denied. She had had a tubal insufflation because of sterility in the past.

Physical examination revealed a pale, well developed and well nourished woman who appeared very tense. Examination of the heart and lungs was negative. The abdomen was slightly distended and showed questionable fullness in the right lower quadrant. There were no masses or tenderness. Peristalsis was moderately increased. A finger specimen of stool was bloody and liquid.

The temperature was 99°F., the pulse 100, and the respirations 16. The blood pressure was 130 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 8.2 gm. per 100 cc. and a white-cell count of 6500, with 88 per cent neutrophils. The red cells showed slight to moderate variation in size, slight polychromatophilia and slight to moderate achromia; occasional cells showed stippling. The platelets appeared normal. The prothrombin time was 12 seconds (normal, 13 seconds). The sodium was 138 milliequiv. and the carbon dioxide 29 milliequiv. per liter; the nonprotein nitrogen was 42 mg., the total protein 5 gm., and the bilirubin 0.2 mg. per 100 cc. Cephalin flocculation was + in twenty-four and forty-eight hours. A gastric aspiration yielded white, mucoid material, which contained no free acid and gave a negative guaiac test. Sigmoidoscopy showed negative bowel for a distance of 18 cm. Above this level the lumen was filled with port-wine-colored, liquid stools.

The patient was repeatedly transfused. On the second hospital day a gastrointestinal series revealed no abnormality in the esophagus, stomach or duodenum. A segment of ileum, 3 cm. in length and 60 to 90 cm. from the ileocecal valve, showed a fairly constant filling defect (Fig. 1). This could not be dislodged despite repeated maneuvering. A barium-enema examination showed a small area of diverticu-

losis near the junction of the descending and sigmoid colon. Just distal to this was a rounded area overlying the sigmoid, which was interpreted as being possibly a diverticulum or polyp. Another small-bowel series on the sixth hospital day failed to reveal a filling defect in the ileum. Stool specimens continued to give ++++ guaiac reactions although the stools were now described as brown and putty-like. On the ninth hospital day the hemoglobin was 13.2 gm. per 100 cc., and an operation was performed.

FIGURE 1. *Film from Small-Bowel Study, Showing a Finger-like Defect in the Lower Ileum (Arrow).*

DIFFERENTIAL DIAGNOSIS

DR. CHARLES G. MIXTER, JR.*: This case is a problem of massive gastrointestinal bleeding of unknown origin. The bleeding apparently was chronic for about a month and then suddenly increased in amount. I think we might see the x-ray films.

DR. JOSEPH HANELIN: The first examination was of the upper gastrointestinal tract and small bowel. There is reasonable assurance from that examination that there was no lesion in the esophagus, stomach and duodenum. A fingerlike defect is present in the ileum approximately 90 cm. from the ileocecal valve, which is about 3 by 1 cm. in size (Fig. 1). It was also seen at fluoroscopy and some spot films were obtained of it. A day or two later a barium-enema examination showed several diverticula of the sigmoid; no polyp was seen. In an attempt to redemonstrate the small-bowel lesion, because such lesions are liable to misinterpretation, we repeated the small-bowel study. At that time no lesion was apparent. However, when the films of the second examination were reviewed, it seemed likely that the small-bowel loops in the area of suspected trouble had not been filled. We contemplated doing still another small-bowel examination, but operation was decided upon before further x-ray studies could be made.

DR. MIXTER: I should like to know exactly what this statement about the barium-enema examination means: "Just distal to this was a rounded area overlying the sigmoid, which was interpreted as being possibly a diverticulum or polyp."

DR. HANELIN: Not infrequently, in the double-contrast examination and sometimes in the post-evacuation colon study, the circular form of a diverticulum will be seen that may simulate the appearance of a polyp.

DR. MIXTER: Would you say that this area noted in the small bowel was consistent with the x-ray picture of an intussusception?

DR. HANELIN: An intussusception may look like that, and if this is an intussusception, there is no indication of the nature of the underlying lesion, which might be a polyp or any number of other possibilities.

DR. MIXTER: I should first like to make a few general statements about the history and the available data. It seems to me that I can explain the dyspnea and profuse sweating on the basis of anemia. The borborygmus over the entire abdomen is consistent with the sudden influx of a great deal of irritating blood into the bowel. The port-wine-colored, liquid stools suggest that the bleeding was probably from higher than the distal large bowel. Certainly, bleeding from the distal half of the large bowel should be bright red in practically all cases. Of particular interest is the fact that there was no history of abdominal discomfort, nausea, vomiting or diarrhea. In view of the fact, therefore, that this appears to have been an intussusception it must have been an intermittent one.

The patient "had had a tubal insufflation because of sterility." I imagine that this is a "red herring," but I tried to connect it with the remainder of the picture. About the only condition that could explain the sterility and bleeding is endometriosis with an implant in the small or large bowel. This patient was fifty-nine years of age and probably had had the menopause. Therefore, though she could have had obstruction from endometriosis in this area, it is practically impossible that she had bleeding from it.

The physical examination was negative except for some confirmatory evidence of anemia and blood in the bowel. The slight fulness in the right lower quadrant suggests slight obstruction. The shift in the neutrophils noted in the smear can be explained, I believe, on the basis of the bleeding into the gastrointestinal tract. The remainder of the laboratory data were negative except for evidence of chronic blood loss. Though she had achlorhydria, the remainder of the picture was not that of pernicious anemia. It can occur in many other conditions. Primary achlorhydria does occur, but it is rare. Again

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the sigmoidoscopy ruled out disease in the last 18 cm. of the distal large bowel.

With those features and the findings in the x-ray examination in mind I believe that I can rule out certain conditions that cause massive gastrointestinal bleeding. Certainly, lesions in the proximal and distal gastrointestinal tract such as varices, atrophic or hypertrophic gastritis, esophageal hernias, peptic ulcers and neoplasms in the esophagus, stomach and duodenum and infections and neoplasms of the colon, at least the distal colon, can be ruled out. Also, there was no information on which to base a diagnosis of any of the various types of hemorrhagic disease, which can give rise to gastrointestinal bleeding. These are usually based on defects in the elements of the blood. Finally, there were no data suggesting that one of the intestinal-tract parasites was to blame. I have thus narrowed the problem down to the lesions that occur in the small bowel and proximal large bowel. I believe I can reduce the possibilities further. In view of the lack of evidence of infection I can rule out regional enteritis, typhoid ulcers, tuberculosis, ulcerative colitis and hemorrhagic or bacillary dysentery, all of which may give rise to massive bleeding. Also, in the absence of pain and of marked symptoms of intestinal obstruction, it seems unlikely that an intussusception that was persistent caused this particular picture. Mesenteric thrombosis is probably unlikely, although mesenteric venous thrombosis can be insidious, prolonged and quite silent in onset.

This leaves me with a rather heterogeneous group of conditions that may conceivably have caused the bleeding. Neoplasms of the small bowel and perhaps of the large bowel frequently bleed, the benign ones being more likely to cause massive bleeding than the malignant ones. The benign lesions are most commonly found in the terminal ileum but can certainly occur in the area that this x-ray film seems to indicate as the source of the trouble. Moreover, they are frequently leading points for intussusceptions, which may reduce themselves and recur. The differentiation of the various types preoperatively is virtually impossible; sometimes, from the x-ray examination, the radiologist can distinguish the benign from the malignant ones.

The rupture of a blood vessel, as a result of either hypertension or arteriosclerosis, and aneurysms have been reported as causing massive gastrointestinal bleeding. An intramural cirsoid aneurysm or the extramural aneurysms of hepatic, splenic, or mesenteric arteries can rupture into the gut. Trauma either externally or internally from a foreign body should be mentioned. Diverticula with or without evidence of diverticulitis occasionally bleed profusely. I recall seeing a patient who had repeated episodes of massive gastrointestinal bleeding for which no cause could be found. At the time of exploration a small diverticulum of the ascending colon, which contained a fecalith, a large eroded blood vessel and a blood clot, was found. That patient has had no bleeding since the diverticulum was removed six years ago. A number of physicians[1] have pointed out that it is not commonly recognized that diverticulitis can result in massive bleeding.

Another lesion to be considered is Meckel's diverticulum or other forms of reduplication of the bowel. Meckel's diverticulum is found in the location of the suspicious area in the small bowel noted in the x-ray examination, but the symptoms more commonly occur in the younger than in the older age group. In some series as many as 60 per cent of them have been reported to cause hemorrhage through peptic ulceration, from aberrant gastric mucosa or as a result of impaired blood supply due to infarcted or intussuscepted bowel. It is possible that, if this was an intussusception, the Meckel diverticulum was leading it. The hemorrhage may be asymptomatic, although it is usually accompanied by pain. The Meckel diverticulum can produce rather puzzling x-ray defects, which change from time to time.

Perhaps I should have paid more attention to the abnormalities in the sigmoid, but they are not so evident in the films as they were described in the protocol. Possibly, the slight evidence for an infectious process should have been emphasized more; I am sure that there are many conditions that can cause massive bleeding that I have not mentioned. Harvey Stone,[1] in an excellent paper on massive melena of obscure origin, classified these cases as those in which a definite cause for the bleeding is found, those in which a lesion is found that may possibly account for the melena and those in which no cause is ever found even sometimes at autopsy. Inasmuch as this is a clinicopathological conference I suspect that this case falls into the first category, and inasmuch as I have to make a choice, I shall say that the patient probably had a Meckel diverticulum.

DR. BENJAMIN CASTLEMAN: Dr. Ali, would you like to comment?

DR. MUNAWAR ALI (from Pakistan): The only thing that I have in mind is an intussusception due to Meckel's diverticulum, which sometimes can give rise to episodes of bleeding.

DR. CASTLEMAN: Dr. Chapman, you followed this patient? Would you like to say a word?

DR. EARLE M. CHAPMAN: Dr. Hanelin discussed with me a third examination, but the anxiety of the patient and her insistence on going home were such a feature in this disease that we believed action had to be forthcoming immediately. Dr. Bartlett and I pressed her to have the operation, and we were indeed pleased at the outcome of it.

DR. WARREN POINT: I have never personally seen or heard of tarry, black stools with a lesion below the ileocecal valve. It seemed to me that the definite history of black, tarry stools almost unequivocally placed the lesion above the ileocecal valve. Since, during the intubation, no blood was found in the stomach juices, we believed that the lesion was below the pylorus and, therefore, that it was a small-bowel lesion of some kind.

Clinical Diagnosis

Polyp of small bowel.

Dr. Charles G. Mixter, Jr.'s Diagnosis

Meckel's diverticulum.

Anatomical Diagnosis

Everted Meckel diverticulum, with mucosal ulceration.

Pathological Discussion

Dr. Marshall K. Bartlett: I should like to emphasize two points. I think it was very astute of those who were taking care of this woman early in her hospitalization to obtain a gastric aspiration. Of course, if the bleeding had stopped, it might have been misleading, but usually it is helpful to have an aspiration done as soon as possible after entry. Also, prompt sigmoidoscopy gave another bit of information that was useful.

It seemed to us that, with the encouragement that Dr. Hanelin had given us and the fact that on two or three occasions the patient had had substantial gastrointestinal hemorrhages, it was safer to explore her than to treat her expectantly as she would have preferred. Our preoperative diagnosis was polyp of the small bowel, which we thought the lesion that Dr. Hanelin had shown us was.

We began our exploration at the ileocecal valve and worked upward for 45 to 60 cm., where we came upon an intussusception of about 7 cm. in length. The leading point of the intussusception was a tubular structure about the size and shape of my little finger within the lumen of the bowel. The intussusception was easily reduced, and the bowel over the base of this intraluminal structure was opened. The lesion was readily recognized as a Meckel diverticulum, which was completely turned inside out. The mucosa at its tip was ulcerated. It was very simple to deal with technically and was excised.

Dr. Mixter: One more point: Stone, in his paper, emphasized that massive bleeding from the gastrointestinal tract of obscure origin had better be treated conservatively unless there is a definite indication for operation such as a demonstrable source for the bleeding or to save the patient's life. We have all seen these patients subjected to an exploratory laparotomy in which every inch of the bowel and the entire abdominal contents are examined thoroughly and yet nothing is found.

Dr. Castleman: The Meckel diverticulum was inverted into the lumen of the bowel and intussuscepted so that the mucosa was on the outside (Fig. 2). The tip seemed like a little tumor, and it was ulcerated. At first glance I thought that this might be a lipoma that was the leading point for an intussusception, but this was because the serosal fat was on the inside. We looked carefully for gastric epithelium, although we did not expect to find any because the ulceration was not of the peptic type.

Dr. Chapman: May I make a comment on Meckel's diverticulum? I had occasion to read Meckel's[2] book, published in 1806. Meckel was the third member of a German family of considerable renown. His father and grandfather had been physicians, surgeons and anatomists. Meckel, the third, described this anomaly to which his name was attached, but if one reads carefully one finds that Meckel did not observe this diverticulum originally. Another man with an unpronounceable name that I have forgotten had described it; Meckel thought it was a "good thing" and publicized it. This often happens in medicine, I am told. Perhaps we do not think of Meckel's diverticulum often enough; 2 per cent of autopsies show a Meckel diverticulum.[3] I had not been aware of this extraordinary frequency of Meckel's diverticulum in the whole population.

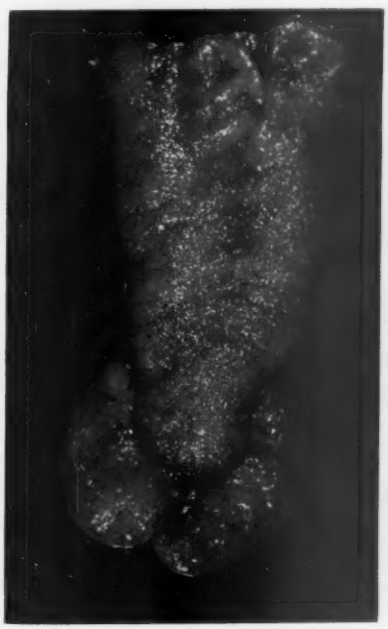

Fig. 2

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VACCINATION AGAINST POLIOMYELITIS

EARLY in 1954[1] in a comment made on the status of research on vaccination against poliomyelitis it was stated that "although no new scientific discoveries are required to determine whether or not a suitable vaccine can be developed for a specific human experiment, a tremendous amount of work by standardized methods was still needed to make certain that the preliminary results of relatively small laboratory tests are sufficiently reproducible to warrant performance of a larger test." The need for standardized and practical methods of production, inactivation and assays for potency and also tests for safety and stability of the finished product, as actually made available on a large scale by different manufacturers, was emphasized. Sabin's[2] concern about the inclusion in the vaccine of the virulent Mahoney strain, minimal amounts of which caused paralysis more readily by the intramuscular than by the intracerebral route, was reiterated.

In addition the possibility of Rh sensitization or kidney lesions resulting from the repeated injections of the small amounts of monkey proteins contained in the vaccines and of inducing reactions in previously sensitized persons by the various constituents of the culture fluid used in making the vaccine, including penicillin and streptomycin, was considered. Such reactions may be expected particularly with the booster doses.

In the spring of 1954, when the first large-scale nation-wide test of the vaccine was started, few observations were available to answer these and other possible objections; those that were available or under way were made chiefly or exclusively in one laboratory and by one group of workers. The need for co-operative studies in different laboratories and by different groups of workers was stressed, as was the "wisdom of making haste slowly."

Before the beginning of the 1954 field trial of the formalin-inactivated vaccine prepared according to his specifications, Salk[3] seemed justified in concluding a presentation of his work on immunization against poliomyelitis as follows:

> The simple fact is: That an experimental method for inducing measurable amounts of antibody for the three known poliomyelitis viruses, employing a killed-virus vaccine is available, and it now becomes possible to determine whether — and to what extent — the incidence of naturally occurring paralysis may be influenced.
>
> All that should be inferred now is that the studies are progressing satisfactorily; there have been no set-backs nor anything but revelations that shed more light on the course ahead. We must continue to regard the experimental developments to date as providing immunologic markers along the way that tell us whether we are on the right road. That there is more to do now than before indicates that we have not stumbled down a by-way but have selected a road, with many lanes, that seem long indeed. Our problem is to select not only the fast lane, but the one that is safest and most certain.

The objective results of the 1954 field trial,[4,5] which, wholly apart from the manner in which the information was first released, was admirably and

carefully planned, controlled and executed, seemed amply to justify Salk's enthusiasm and to indicate that he had chosen not only a fast lane but also one that was safe and reasonably certain. Moreover, in the opinion of the experts chosen to evaluate them, these results also appeared to justify the release, for general use, of vaccines produced by several manufacturers according to Salk's specifications. Those who may have objected to any of the procedures as inadequate in theory, or who were dissatisfied with the lack of sufficient data on any given aspect of safety or efficacy, were either not heard or were seemingly persuaded by the compelling argument of the practical and large-scale performance. Some major defects in certain preparations due to what may have seemed to be minor or unimportant deviations from the method — such as the progressive loss of potency after Merthiolate was added as a preservative — were recognized and presumably corrected.[6] Other changes in methods of production had been introduced deliberately — for example, the concentration of formalin and the temperature and time at which it is permitted to act,[7] — with perhaps inadequate controls (if, indeed, adequate methods for such controls were available) on the exact effects of the procedures as carried out during large-scale production.

The events that have followed the use of the Salk vaccines since the middle of April, 1955, have been publicized almost entirely through the public press and over the air through radio and television. The essentials for scientific evaluation of these events — namely, adequate and carefully documented data that permit leisurely and critical analysis — were unfortunately still lacking.* However, the Weekly Communicable Disease Summaries issued by the National Office of Vital Statistics of the United States Public Health Service for each of the ten weeks ending June 25, reveal some interesting figures on the occurrence of poliomyelitis in the United States. Despite the known limitations of such current figures, they are worthy of review and analysis.

For this entire period there was an appreciably smaller total number of cases of poliomyelitis, and 11 per cent fewer cases of paralytic poliomyelitis reported throughout the country than for the corresponding ten weeks of 1954. However, for each of the first six weeks of this period (from the week ending April 23) the total number of cases was greater, and for five of these six weeks more paralytic cases were reported in 1955 as compared with the corresponding weeks of the previous year. For most of the reporting states, and particularly for California and Texas, which reported the largest numbers of cases in each of the two years, fewer cases were reported during each week in 1955 as compared with the corresponding one in 1954. Exceptions were the states of Illinois and New York, in which a greater total number of cases as well as more paralytic cases were reported each week; Idaho and Pennsylvania reported more cases, but few or none with paralysis, whereas Louisiana and Georgia reported more cases and more paralytic cases in each of four or more weeks consecutively in 1955, mostly during May.

Since the beginning of the current poliomyelitis "disease year," or about April 1, 11 widely scattered states were 20 per cent or more in excess in the number of cases reported than for any similar period during the previous three years. Only 5 states, mostly in the South, reported numbers 20 per cent or more below the lowest numbers for the previous three years. Obviously, none of these figures, by themselves, can be considered as accurate or can be interpreted as having any significance so far as the vaccination program is concerned.

Of particular interest, however, are the data from the Poliomyelitis Surveillance Unit of the Communicable Disease Center in Atlanta, Georgia, as recorded in some of the same weekly reports. This unit has accepted reports of a total of 107 paralytic and 67 nonparalytic cases among vaccinated persons through June 28 of this year. In the same period it has also accepted 114 cases of paralytic and 35 of nonparalytic poliomyelitis among family and community contacts of vaccinated persons. Particularly noteworthy is the fact that 27 of the first 64 cases of paralytic poliomyelitis in family contacts involved parents of vaccinated children. The cases among vaccinated persons were from 30 states and territories, and those from contacts of vaccinated persons were from 22 states, 1 territory and the District of Columbia.

Poliomyelitis viruses were isolated from 32 of the vaccinated patients, from 22 of the cases among family contact and from 5 of those in community contacts. Except for 2 strains of Type 2 and 1 of Type 3 isolated from vaccinated patients all the strains of poliomyelitis virus isolated from both vaccinated patients and from the contact cases were identified as Type 1.

The paralytic cases accepted by the Poliomyelitis Surveillance Unit represent about a fourth of all the paralytic cases and about 15 per cent of all the cases of poliomyelitis reported for the ten-week period under discussion. Since no breakdown of the cases by age is presented in these weekly reports, and since the vaccinated patients represented a relatively narrow age group, it may be assumed that these totals for the paralytic cases among vaccinated persons represent a still higher proportion of the same age group.

The brief period between the vaccination and the onset of paralysis in the vaccinated cases, the frequency with which the onset of paralysis occurred in the extremity where the vaccine had been injected, the appreciably longer interval between vaccination of persons and the onset of symptoms of paralysis in cases among their contacts, the paucity or absence of

*These were detailed in the "Technical Report on Salk Poliomyelitis Vaccine" by the Surgeon General of the United States Public Health Service to the Secretary of Health, Education and Welfare on June 10, 1955.

other cases in the same areas or population groups among persons not vaccinated and not intimately exposed to vaccinated persons and, finally, the demonstration of living virus in the cases among the vaccinated patients and their contacts all point to the presence of live, virulent, paralytogenic viruses in some lots of vaccine that were given for protection against paralytic poliomyelitis, and implicating primarily the Type 1 component of the vaccine, but also possibly the other types.*

It seems abundantly clear that the specifications for a poliomyelitis vaccine that would be safe, effective and suitable for general use, as expressed by some of the foremost workers in the field,[5-12] were not adequately satisfied by all the lots of formalinized vaccine that were commercially produced and released in the spring of 1955. It is, of course, of the utmost importance to probe deeply and intimately into all the possible reasons for these unfortunate events, which constitute a serious setback in the program for the prevention of poliomyelitis with what Salk had chosen to call a "killed-virus" vaccine.[3]

Regardless of the motives that prompted the strong pressures for the hasty and perhaps premature release of this product, it is unthinkable that, in retrospect, the same persons who consented to the release of the vaccine last April would have done so if they had considered that there was a definite potentiality for the production of so many cases of paralytic poliomyelitis by vaccination, even if this is considered a relatively small number in relation to the possible number of cases that might eventually develop among all those who received the vaccine. Obviously, the conditions that result in a small number of cases from any given lot or lots may recur at another time, in a more serious form and in a larger number of lots; such an occurrence could spell disaster — unless the specific causes of the difficulties in the defective lots are discovered and remedies for the correction of the defect are found and successfully applied.

Since, as far as one can ascertain, no specific causes for the defective lots have been decisively established, or at least revealed, it seems doubtful if any vaccine made and tested by the same methods as those previously used can be considered truly safe. Certainly, merely multiplying the controls can only reduce but not eliminate the possibility of encountering the same difficulty. Radical changes in the method and specifications for the vaccine therefore seem to be called for. One that has already been recommended and unanimously accepted, in principle, is the substitution in the vaccine of a different Type 1 strain with less potentialities for producing paralysis when injected intramuscularly, as compared with the Mahoney strain that was used in the 1954 and the early 1955 vaccines and may be assumed to be responsible for almost all the paralytic cases in the vaccinated persons and for all those among their contacts.

The entire problem could now profitably be restudied in a more fundamental manner. The status of the inactivated-virus vaccine in the prevention of poliomyelitis must still be considered experimental. Perhaps other types of vaccine, notably those utilizing live attenuated viruses, which have been considered potentially superior to the killed vaccine by many experts,[9-14] may be studied and tested more thoroughly and on a scale warranted by preliminary and adequate preparations, controls and safeguards. Some of the proponents of the attenuated live-virus vaccines could now justifiably point to the cases of poliomyelitis resulting from the recent vaccinations as indicating that the antibody and protection produced by the so-called inactivated or "killed" vaccine was indeed the result of the residual live virus, or possibly the result of a reversal to active live virus within the body of at least a portion of the injected virus.

At the moment it is far from clear whether the march of progress in vaccination against poliomyelitis has stumbled down a by-way or is proceeding hesitatingly on the long and proper path because it has chosen to follow a lane that is both too fast and too uncertain. Perhaps the greatest misfortune that could result from the serious difficulties encountered with the Salk vaccine during this year could be the adverse "effect of this undertaking on the entire field of scientific investigation and on the public confidence upon which it depends," as stated by Francis[8] about the use of any given preparation that is selected for a large-scale field trial and the possibility that failure to demonstrate a protective effect by that particular preparation might result in a challenge to the basic principle of the vaccine rather than to an inadequate product. There is the same or even greater concern in the matter of the safety of any product released, for it would be unfortunate indeed if the public lost confidence in the methods of testing and control that are applied to ensure the safety of products released for use in preventive vaccination.

The intensive investigations and continued vigilance of the United States Public Health Service and the admirable co-operation offered by the commercial manufacturers since the difficulties with the vaccines were first recognized are detailed in the Surgeon General's "Technical Report" of June 10. They reflect great credit on the Public Health Service and the manufacturing industry and, with the adoption of the legislation recommended, should eventually serve to restore confidence and permit the orderly development and use of an effective and safe vaccine.

*Live poliomyelitis (Type 1) virus was demonstrated in samples of commercial vaccine released to the Idaho State Health Department according to a statement by Dr. Louis P. Gebhardt, of the University of Utah, quoted in an Associated Press dispatch and mentioned in the Surgeon General's "Technical Report" of June 10, 1955.

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APPOINTMENT IN ISRAEL

THE third World Medical Assembly of Jewish physicians, to be held in Israel under the auspices of the Israel Medical Association from August 10 to 21, will commemorate, in a way, the life and death of Maimonides. For the birth of this great Jewish physician and philosopher, author of *Guide to the Perplexed* and personal physician to Saladin took place in Cordova eight hundred and twenty years ago last March, and the seven hundred and fiftieth anniversary of his death occurred in December, 1954. The lapse of seven and a half centuries has rather added luster to his name than dimmed it.

It is expected that the assembly, under the patronage of President Itzhak Ben Zvi of Israel, will be widely attended, more than 27,000 physicians in the United States alone having been invited to participate. The meeting will convene in Haifa on August 10 with an opening address by the Israeli minister of health, to be followed by a scientific program by Israeli physicians and scientists on problems of health peculiar to Israel. After four days the group will move to Tel Aviv, where it will be welcomed by the Tel Aviv branch of the Israel Medical Association and members of the American embassy. The second phase of the meeting will consist of a three-day scientific program by various visiting physicians.

The scientific sessions will be punctuated by the usual receptions, and at their close a week will be devoted to a tour of the country. It will be noted that American participation in the assembly will be under the auspices of the American Physicians Fellowship Committee, Incorporated, of the Israel Medical Association, with national offices in Nashua, New Hampshire.

Such gatherings, becoming each year more numerous and more representative, are further evidence of the spread of an internationalism that will yet save the world from a misunderstanding and distrust that no nation really desires to perpetuate.

COMMITTEE OF AMERICAN ACADEMY OF PEDIATRICS REPORTS ON POLIOMYELITIS VACCINE

THE Committee on the Control of Infectious Diseases of the American Academy of Pediatrics, in the process of bringing up to date the Academy's inclusive brochure on this subject, has taken time out to consider the important matter of poliomyelitis immunization. This was done at a special meeting held at the Chateau Frontenac, Quebec, on June 15, 1955.

After due discussion the following resolution was unanimously adopted by those present:

> In view of the difficulties which have arisen with respect to the manufacture, testing, and usage of large volumes of poliomyelitis vaccine, particularly in regard to its safety and potency; and in view of the rapid approach of the polio season in most parts of the country, the Committee for the Control of Infectious Diseases of the American Academy of Pediatrics recommends that injections of this vaccine be discontinued for the present.

Druggists should refuse opium and its preparations to persons suspected of suicidal intent.
Boston M. & S. J., *August 2, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

MASSIVE PULMONARY EDEMA CAUSED BY EXCESSIVE ADMINISTRATION OF EPINEPHRINE

A twenty-seven-year-old registered nurse, a gravida II, para I, had had a classic cesarean section sixteen months previously by the present surgeon for cephalopelvic disproportion after a failed test of labor. She then moved to a distant city, reappearing two and a half weeks before term to request a repeat cesarean section from the same surgeon. She stated that she had been under a doctor's care, and that her pregnancy had been normal. The surgeon took her blood pressure but made no other test or examination, accepting her statement as fact, and scheduled the operation for a date two weeks from term. A physician anesthetist elicited a story of transfusion with 500 cc. of packed red cells seven weeks earlier. He ordered a urinalysis (which was negative), determination of hemoglobin (10.7 gm. per 100 cc.) and crossmatching, as well as appropriate preoperative measures for the next morning.

The patient went into labor about nine hours after admission (10:20 p.m.), and the operation was done at midnight under spinal anesthesia with no preoperative medication. After delivery, a full ampoule of

epinephrine was mistakenly given in place of oxytocin, and, in fact, the mistake may have been repeated. Extreme levels of blood pressure and pulse resulted, and fibrillation was suspected at one point. These symptoms were appropriately treated, with good effect, but massive pulmonary edema occurred immediately after operation. This too improved under treatment by the anesthetist but recurred four hours later and was again treated by the anesthetic staff (day shift) and by a cardiac consultant. Their efforts failed, and the patient died about twelve hours after operation. She had received 500 cc. of blood and at least 1000 cc. of fluids intravenously during and after the operation; in fact, this infusion was not stopped until two hours after signs of pulmonary edema developed for the second time.

Autopsy showed massive pulmonary edema but no other anatomic changes.

This was classified as a preventable death. The primary avoidable factor, of course, was the accidentally administered dose of epinephrine combined with a moderate anemia in the presence of what seems to have been certainly no less than average blood loss for the operation involved.

There seems to be some question whether even a double dose of this medication alone would have been fatal, but in the absence of other factors apparent from the study it is regarded as the cause of death. However, it is deplorable that physical examination and history (of packed-red-cell infusion) were left to the anesthetist. One wonders how severe an underlying anemia was present despite laboratory findings that were not too alarming. More than one patient has been drowned by the overadministration of fluids intravenously, and although such an effect may not have been present in the case under discussion, the observation is inescapable that fluid kept running two hours after edema of the lungs was obvious and that a competent consultant was not obtained until more than two hours after the patient was apparently in serious trouble for the second time.

In other words an accident proved fatal that, with more assiduous and intelligent management, might have been corrected.

JOHN FIGGIS JEWETT, M.D.
Chairman

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additonal information in regard to all listed books will be gladly furnished on request.

Reproductive System: A compilation of paintings on the normal and pathologic anatomy. Vol. 2. Prepared by Frank H. Netter, M.D. Edited by Ernst Oppenheimer, M.D. With a foreword by John Rock, M.D., clinical professor of gynecology, Harvard Medical School. 4°, cloth, 286 pp., with colored plates. Summit: Ciba Pharmaceutical Products, Incorporated, 1954. $13.00. *(Ciba Collection of Medical Illustrations.)*

This is the second volume of a series of colored atlases designed to portray the anatomy and pathology of the human body. (The first, which was devoted to the nervous system, soon went out of print and probably will be reprinted.) The illustrations and text concern the normal anatomy and pathology of the male and female reproductive systems. There is a good index, and the publishing is excellent. The volumes are sold at cost and should be in all medical libraries.

The Skin: A clinicopathologic treatise. By Arthur C. Allen, M.D., associate pathologist, Memorial Hospital, associate professor of pathology, Cornell University Medical College, associate attending pathologist, Memorial Cancer Center, New York City, Sloan–Kettering Division, Bronx Veterans Administration Hospital, and consulting pathologist, New York Infirmary. 4°, cloth, 1048 pp., with 495 plates. St. Louis: C. V. Mosby Company, 1954. $25.00.

This semiatlas with descriptive text covers the whole field of dermatology. The literature has been surveyed, and lists of references are appended to the chapters. The illustrative work and the publishing in general are excellent. The price is not excessive for this type of atlas. The book should be in all collections on diseases of the skin.

Standard Values in Nutrition and Metabolism: Being the second fascicle of a handbook of biological data. Edited by Errett C. Albritton, M.D., Fry Professor of Physiology, George Washington University. 4°, paper, 380 pp., with tables. Philadelphia: W. B. Saunders Company, 1954. $6.50. (Prepared under the direction of the Committee on the Handbook of Biological Data, American Institute of Biological Sciences, National Research Council.)

This valuable reference book is the joint work of over 800 contributors. The tables cover the whole field of nutrition and metabolism. There is a comprehensive bibliography of 109 pages and a good index. The book is recommended for all medical libraries and to all interested persons.

NOTICES

SOCIETY MEETINGS AND CONFERENCES

JULY, AUGUST and SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.

AUGUST 4–AUGUST 23. Consultation Clinics for Crippled Children in Massachusetts. Page 1099, issue of June 23.

AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.

AUGUST 30 and 31 and SEPTEMBER 1. New England Health Institute. Page 1010, issue of June 9.

SEPTEMBER 12–21, DECEMBER 5–14, 1955, JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

SEPTEMBER 30–OCTOBER 1. American Medical Writers' Association. Page 118, issue of July 21.

OCTOBER 1 and 2 and 3–6. American Academy of Pediatrics. Page 118, issue of July 21.

OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.

OCTOBER 10–21. New York Academy of Medicine. Graduate Fortnight. Page 84, issue of July 14.

OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.

OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.

OCTOBER 26, NOVEMBER 30, 1955, JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.

NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

NOVEMBER 7–9. Association of Military Surgeons of the United States. Page 118, issue of July 21.

NOVEMBER 11 and 12. Inter-Society Cytology Council. Page 1056, issue of June 16.

NOVEMBER 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

NOVEMBER 29–DECEMBER 2. Interim Session of the American Medical Association, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, AUGUST 4

THURSDAY, AUGUST 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

(Concluded on page xviii)

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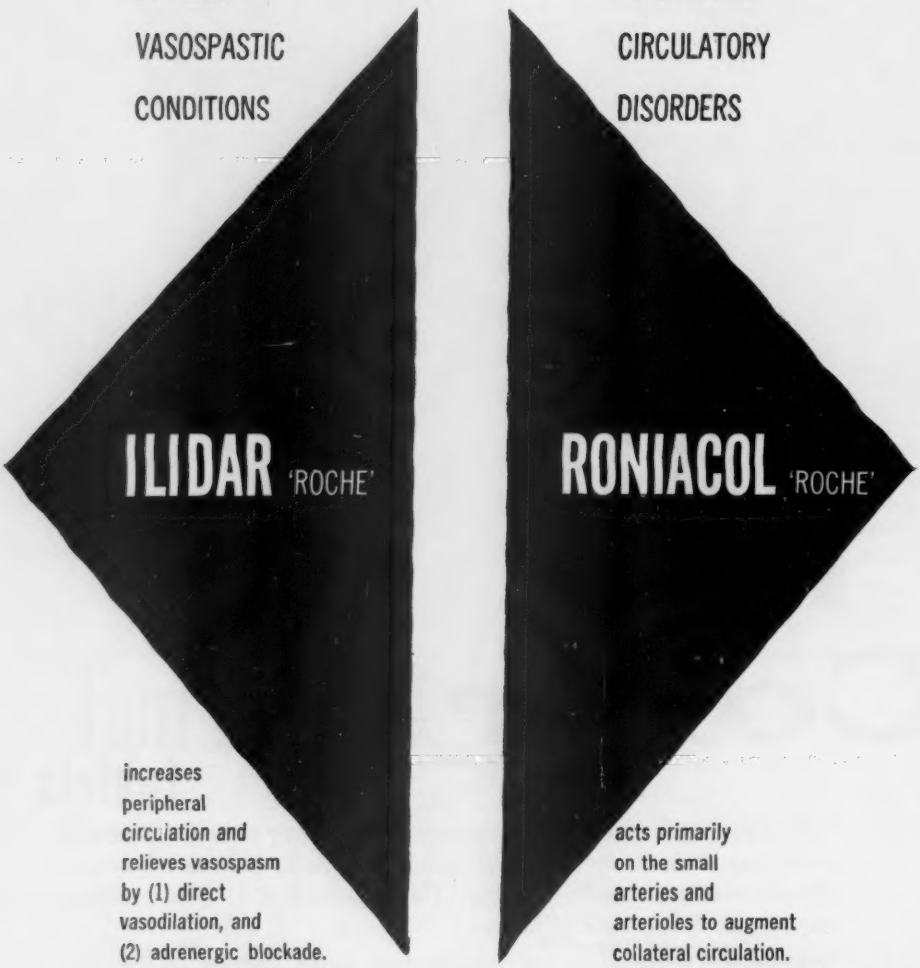

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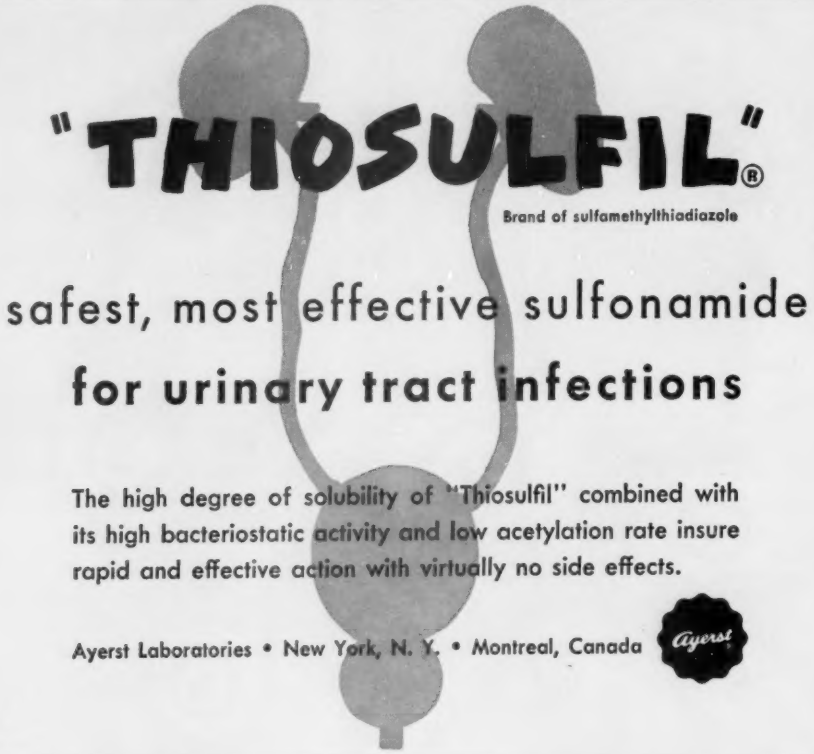
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(Concluded from page 158)

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Thoracic Conference. Atrial Septal Defects. Dr. Walter T. Goodale. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, AUGUST 5
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, AUGUST 6
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, AUGUST 8
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, AUGUST 9
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, AUGUST 10
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m –1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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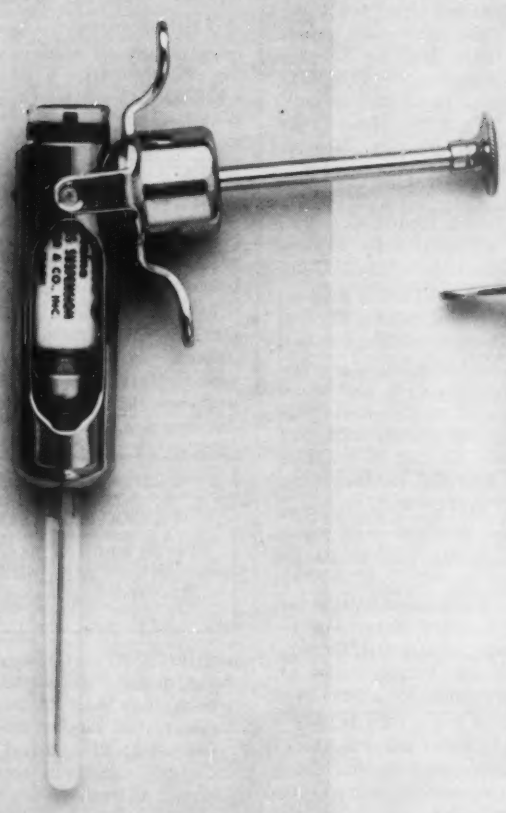

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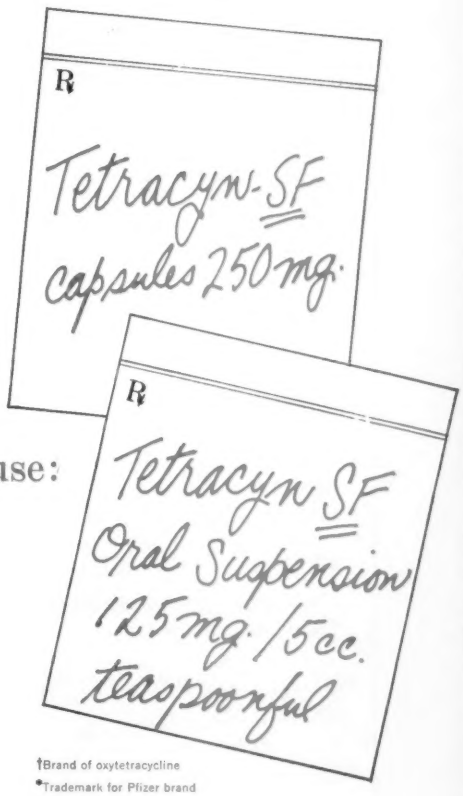

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1. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared in Collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Washington, D. C., 1952. 2. Martí-Ibáñez, F.: Antibiotic Med. *1*:247 (May) 1955. 3. Dumas, K. J.; Carlozzi, M., and Wright, W. A.: Antibiotic Med. *1*:296 (May) 1955. 4. Milberg, M. B., and Michael, M., Jr.: Ann. New York Acad. Sc., In press. 5. Prigot, A.: Ibid.

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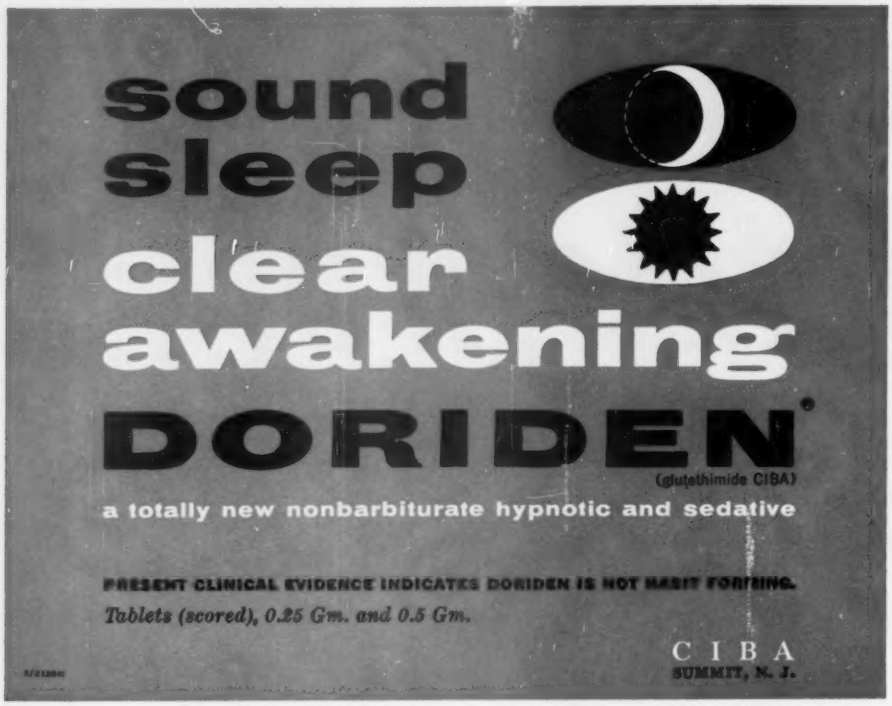

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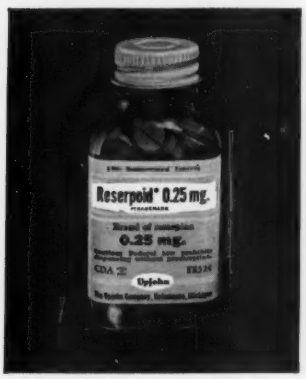

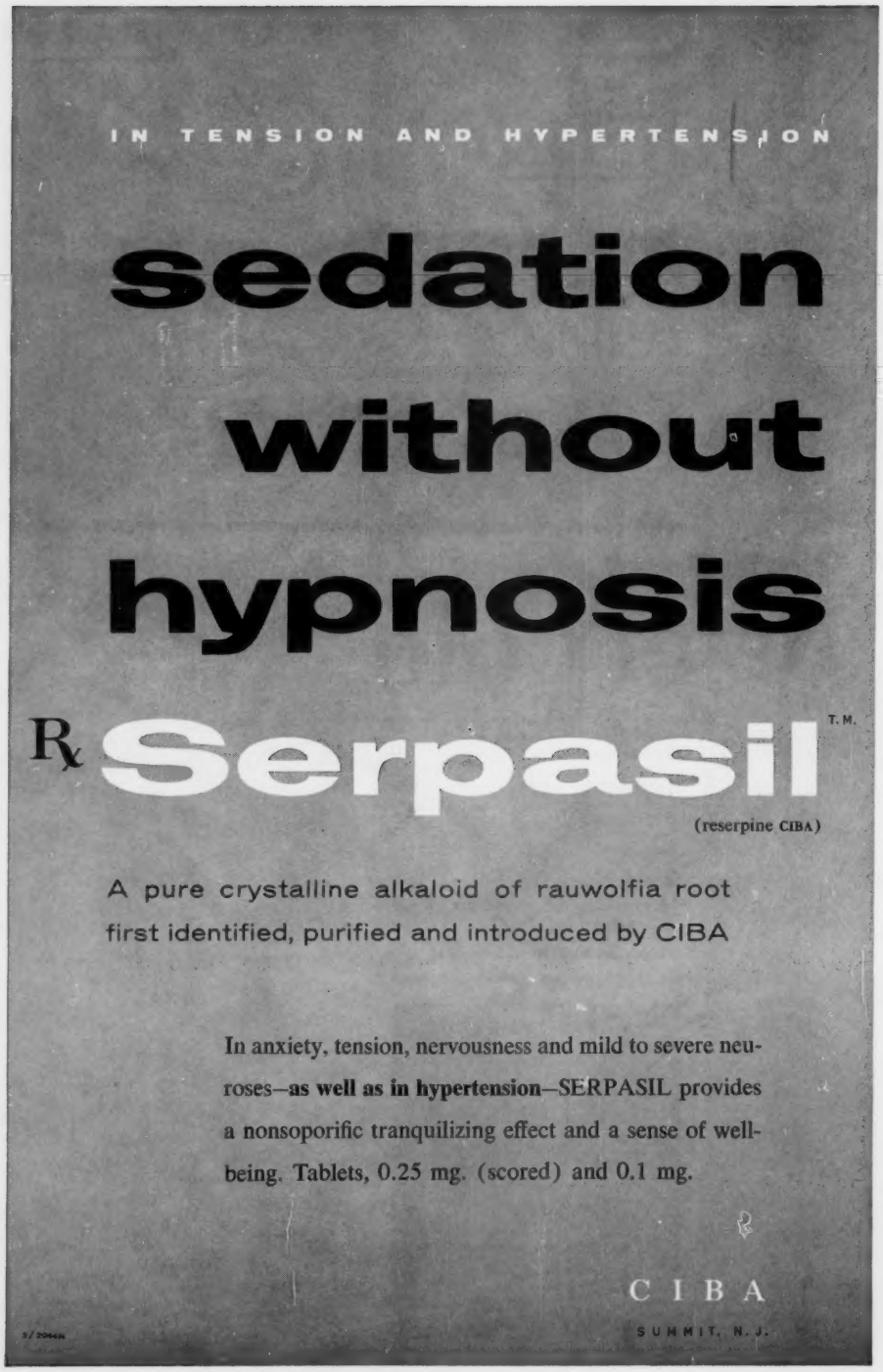
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